Non-seminimatous germ cell tumors of the testis. Staging and threatment (An anlysis of the results of the treatment of 103 patients in the clinical stages I and II during the period 1963-1977).

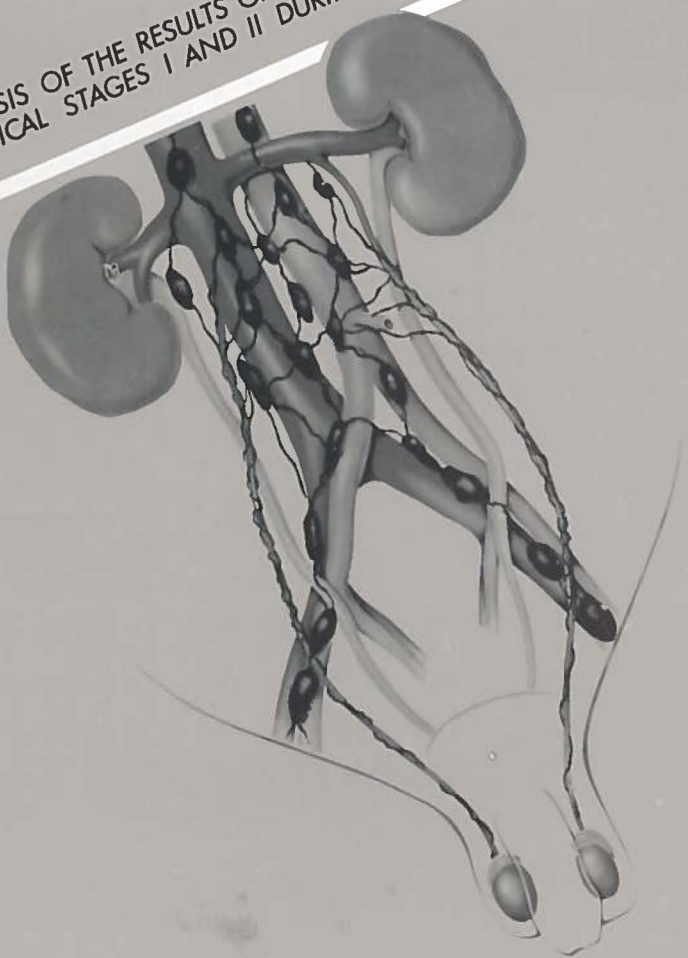
Wobbes, Theo

TH. WOBBES

NON-SEMINOMATOUS GERM CELL TUMOURS OF THE TESTIS

STAGING AND TREATMENT

ANALYSIS OF THE RESULTS OF THE TREATMENT OF 103 PATIENTS IN THE CLINICAL STAGES I AND II DURING THE PERIOD 1963–1977



NON-SEMINOMATOUS GERM CELL TUMOURS OF THE TESTIS

staging and treatment

(An analysis of the results of the treatment of 103 patients in the clinical stages I and II during the period 1963-1977)

STELLINGEN

I.

De behandeling van een patient met een niet-seminoom kiemceltumor van de testis dient in een centrum te geschieden, waarin per jaar minstens 20 patienten met een dergelijke afwijking worden behandeld.

II.

De enig betrouwbare methode om het effect na te gaan van combinatie chemotherapie bij een patient met een niet-seminoom testistumor, is het verwijderen van de tumorresten voor histologisch onderzoek, hetzij door een laparotomie hetzij door een thoracotomie.

III.

Bij kinderen met een infantiel embryonaalcelcarcinoom bepaalt de leeftijd de behandelingswijze.

IV.

Indien een niet-seminoom kiemceltumor van de testis pulmonaal is gemetastaseerd moet een CT-scan van de hersenen worden vervaardigd.

V.

De oppervlakkige parotidectomie voor het pleiomorf adenoom is geen oncologische operatie.

VI.

Het is zeer waarschijnlijk, dat de mogelijkheid mammasparend te zijn bij de behandeling van het mammacarcinoom stimulerend werkt op het zelfonderzoek en het vroegtijdig zoeken om medische hulp.

VII.

Het is wenselijk van de laparotomiewond bij een colonoperatie alleen de fascie primair te sluiten.

VIII.

Als toegangsweg voor de toediening van cytostatica heeft de end to side fistel tussen de vena cephalica en de arteria radialis de voorkeur.

IX.

Patienten met een maligne melanoom moet het roken worden ontraden.

X.

De geur van patienten met een zogenaamde "smelly tumour" is effectiever te verdrijven met behulp van het oraal gebruik van metronidazole dan door het sprayen met een deodorant.

XI.

Bij iedere zwangere behoort éénmaal een echografisch onderzoek te worden verricht.

XII.

De mensheid toont vele kenmerken van een kwaadaardig gezwel. Voor de behandeling schijnt zij zelf de voorkeur te geven aan radiotherapie.

Stellingen
behorende bij het proefschrift van
Th. Wobbes
Non-seminomatous germ cell tumours of the testis, staging and treatment
Groningen, 1981

RIJKSUNIVERSITEIT TE GRONINGEN

NON-SEMINOMATOUS GERM CELL TUMOURS OF THE TESTIS
staging and treatment

(An analysis of the results of the treatment of 103 patients in the clinical stages I and II during the period 1963-1977)

PROEFSCHRIFT

ter verkrijging van het doctoraat in de Geneeskunde
aan de Rijksuniversiteit te Groningen
op gezag van de Rector Magnificus Dr. L. J. Engels
in het openbaar te verdedigen op woensdag 18 november 1981
des namiddags te 4.00 uur
door

THEO WOBBES

geboren te Groningen

1981
DRUKKERIJ VAN DENDEREN B.V.
GRONINGEN

Promotor: Prof. Dr. H. Schraffordt Koops
Copromotor: Prof. Dr. J. Oldhoff
Coreferent: Dr. R. Eibergen

ACKNOWLEDGEMENTS

This thesis was performed in the Division of Surgical Oncology (Head: Prof. Dr. J. Oldhoff) of the Department of Surgery (Head: Prof. Dr. P. J. Kuijjer) of the University Hospital, Groningen, The Netherlands.
I would like to express my sincere appreciation to Prof. Dr. H. Schraffordt Koops, Prof. Dr. J. Oldhoff and Dr. R. Eibergen for all their invaluable help and stimulating criticism in the preparation of this manuscript.
The histological specimens were revised by Dr. R. Eibergen, pathologist to the Roman Catholic Hospital, Groningen, who was at the time pathologist to the Department of Pathology of the State University Groningen (Head: Prof. Dr. Ph. J. Hoedemaeker).
The lymphograms were revised by Dr. J. M. H. Blom, radiologist at the Military Hospital "Dr. A. Mathijsen", Utrecht.
Mr. L. Th. van de Weele (Computer Centre, State University, Groningen) considered the suitability of the material for statistical analysis.
Mr. Th. van Winsen translated the manuscript and P. H. Robinson F.R.C.S. made some corrections and completed the translation.
Technical illustrations were made by Drs. H. J. ten Duis, the other drawings and cover design were skillfully carried out by D. Buiter, medical artist to the Department of Neurosurgery (Head: Prof. Dr. J. F. W. Beks). The photograph was made by the Department of Medical Photography.
The manuscript was typed by Miss M. L. W. Hermans and Miss M. J. Schmidt.
Miss C. Koppe, Miss H. Q. Ydens and Mr. R. Houtman assisted in other administrative affairs.
My greatful thanks are due to all persons for all their help and interest in the completion of this dissertation.

To Margriet and Ritse

CONTENTS

„Le traitement radical des tumeurs testiculaires malignes comporte théoriquement l'ablation du testicule néoplasique, de ses voies lymphatiques, et des ganglions auxquels ces voies aboutissent."

(Chevassu 1906)

CHAPTER I

INTRODUCTION

Malignant testicular tumours represent only a small proportion of all human malignancies. Since they develop mainly at an early age, however, they are a frequent challenge to the specialist in charge. The treatment of patients with tumours of this group has shown unmistakable progress in the past decade, and consequently the prognosis is now better than that of many other malignant neoplasms.

While it is generally agreed that a patient with a seminoma requires treatment by orchiectomy and radiotherapy, the treatment of non-seminomatous tumours is still decidedly controversial. Orchiectomy is of course required but the subsequent treatment of the retroperitoneal lymph nodes is a controversial subject. Is retroperitoneal lymph node dissection required for staging and treatment, or should these nodes be submitted to radiotherapy or chemotherapy?

It is difficult to compare groups of patients treated by node dissection with those treated by radiotherapy. The advocates of primary radiotherapy, after all, base themselves solely on radiological findings; and the limitations of diagnostic radiology leave uncertainty about the stage of the disease which the patient has reached. On the other hand, a laparotomy and if possible retroperitoneal lymph node dissection supply exact information on the true regional metastatic spread. Experience with chemotherapeutic treatment of retroperitoneal metastases is still limited.

Due to the low incidence of malignant testicular tumours, it is hardly

possible in one centre to gain sufficient experience to outline the treatment of choice. This would require a prospective randomized study, and no such study has so far been published. Consequently a definite answer to the question of the treatment of choice cannot yet be given.

This thesis focuses mainly on two aspects of the approach to non-seminomatous germ cell tumours of the testis: staging and surgical treatment. The results presented are based on a retrospective study of the findings obtained in 103 patients in clinical stages I and II, i.e. exclusively patients in whom the tumour was limited to levels caudal to the diaphragm. These patients were treated by the Division of Surgical Oncology, Groningen University Hospital, during the period 1963-1977. Laparotomy and, if possible, retroperitoneal lymph node dissection was performed in all cases. The follow-up on these cases covered a period of at least three years.
With regard to staging, efforts were made to establish whether the extent of the primary tumour is of prognostic significance. Secondly, the value of lymphography was studied as compared with the findings at operation and/or histological examination. With regard to treatment, the contribution of laparotomy and retroperitoneal lymph node dissection to the results was studied. The role of adjuvant chemotherapy in stage II was likewise considered. In some of the stage II patients, lymph node dissection was followed by irradiation of the retroperitoneum and adjuvant actinomycin-D over a period of two years. Others received only adjuvant actinomycin-D. In addition to the therapeutic results, the operative complications are described.
Chapters II through VI attempt to present an outline of the discussion in the literature on the treatment of patients with non-seminomatous tumours of the testis.
This study was not designed as an attempt to demonstrate the superiority, if any, of primary surgical treatment of non-seminomatous tumours. As already mentioned, this would be impossible. However, an attempt was made to present and discuss the backgrounds and the results of the therapeutic approach made by the Division of Surgical Oncology of the Department of Surgery, University Hospital, Groningen.

CHAPTER II

GENERAL DATA ON TESTICULAR TUMOURS

II.1 Epidemiology

Although testicular tumours represent only 1-2% of all malignant human tumours, they are the most common malignancy in males aged 29-35 years (Javadpour 1978).

The incidence of testicular tumours is not the same in all countries and population groups. While in the USA and England the incidence is about 2-3 per 100,000 males (Dixon and Moore 1953; Collins and Pugh 1964), it is 0.9 in Finland (Teppo 1973) and 4.5 in Denmark (Clemmesen 1968). In negroid races, however, the incidence is much lower. Zimmerman and Kunj'u (1978) found an incidence of 0.08 in Kenya, and Rao and Sparke (1979) reported an incidence of 0.4 in Jamaica. The cause of these differences in incidence has remained obscure.

The figures in The Netherlands correspond with those in the USA and England, but a slightly higher incidence is found in rural areas. Talerman et al. (1974) reported an incidence of about 2.5 in The Hague and Rotterdam, while that in the province of Friesland was 4.2. Other authors have likewise reported a predominance of testicular tumours in rural areas (Lipworth and Dayan 1969), but Clemmesen (1968) and Graham and Gibson (1971) reported exactly the opposite: a higher incidence in big cities. The latter authors, moreover, found more testicular tumours in protestants than in catholics - a finding previously reported also by Grumet and MacMahon (1975).

II.2 Histology

Two groups of testicular tumours are distinguishable histologically: germ

cell tumours and non-germ cell tumours. Germ cell tumours account for about 96% of all testicular tumours. The other neoplasms arise from interstitial tissue: Leydig cell tumours and Sertoli cell tumours. In addition there are gonadoblastomas, which contain germ cells as well as interstitial components.
Malignant lymphoma is the most common secondary tumour with primary manifestation in the testis. Occasionally, metastases of another primary tumour are found in the testis (Mostofi and Price 1973). Partly for practical reasons, testicular germ cell tumours are divided into seminomas and non-seminomatous tumours. The latter group comprises embryonal carcinomas, teratomas and choriocarcinomas. Some 40% of all testicular tumours are combinations of the various histological types. A more detailed discussion of the histological classifications is to be presented in chapter V.

II.3 Age

Testicular tumours can develop at any age, but become manifest most frequently at age 30-34 (Graham and Gibson 1972). Seminomas develop about five years later than non-seminomatous tumours. Testicular tumours are rare in childhood, but a distinct peak is observed before the third year of life. The latter neoplasms are probably congenital. Whereas in adults germ cell tumours account for 96% of all testicular tumours, this percentage is only 67 in children. Infantile embryonal carcinomas (yolk-sac tumours, endodermal sinus tumours, orchioblastomas, adenocarcinoma of the infantile testis, adenocarcinomas with clear cells) are the most common tumours in childhood, followed by teratomas (Brosman 1979; Wobbes et al. 1981b). Seminomas and choriocarcinomas do not develop in the first 10 years of life (Mostofi and Price 1973).
Germ cell tumours are found also in patients aged over 50, but in this age group malignant lymphomas are the most common tumours (Mostofi and Price 1973).

II.4 Aetiological factors

II.4.1 *Undescended testicle*

The mechanism underlying the development of a malignant testicular tumour has so far remained obscure. The only unmistakable correlation is that with an undescended testicle. LeComte (1851) was probably the first to

mention the correlation between an undescended testicle and a malignant testicular tumour. He wrote: „La présence du testicule dans une région qui lui est étrangère est souvent une infirmité, et peut déterminer des accidents graves. Cet organe peut s'enflammer, s'altérer, dégénérer, et présenter les diverses affections dont le testicule, descendu dans les bourses, est atteint". ("The presence of a testicle in an area which is strange to it is often a disability, and may cause serious complications. The organ may become inflamed, change, degenerate, and also present the various affections to which the descended testicle can be subject".)

The literature shows that 3-12% of all testicular germ cell tumours develop in undescended testicles. In a group of 230 patients treated in the departments of Surgical Oncology and Radiotherapy of the Groningen University Hospital, this percentage was 5.2 (Wobbes et al. 1980a). This study revealed that the risk of developing a malignant testicular tumour in males with an undescended testicle or treated for an undescended testicle by orchiopexy, was 17 times as high as that in males with normally descended testicles. Gilbert and Hamilton (1940) even found a 48-fold increased risk. A testicle localized within the abdomen is five times more likely to show malignant degeneration than an inguinally localized testicle (Martin and Menck 1975). The risk of malignant degeneration in the contralateral, normally descended testicle is likewise increased (Gehring et al. 1974).

The cause of the increased risk of malignant degeneration in an undescended testicle is unknown. Until a few years ago it was thought that the higher temperature in the abdomen or in the inguinal canal might be responsible, but this theory has been abandoned because malignant degeneration is frequently observed also after orchiopexy (Witus et al. 1959; Altman and Malament 1967; Wobbes et al. 1980a).

Dysgenesis of the genital system is currently accepted as a possible cause (Haines and Grabstald 1950). This would also explain the increased frequency of malignant tumours in the contralateral, normally descended testis. The diminished fertility may also be related to the dysgenesis. Findings of interest in this context were reported by Skakkebæk and Berthelsen (1978), who identified carcinoma-in-situ in nine out of 18 testicular biopsy specimens from 15 infertile men. In the same group of investigators, Krabbe et al. (1979) reported that a carcinoma-in-situ was found in the seminiferous tubules in 8% of men previously treated for an undescended testis. Another finding possibly related to the dysgenesis is that some authors reported a slightly higher incidence of congenital inguinal hernia in the history of pa-

tients with a malignant testicular tumour than in a normal population. Morrison (1976) found inguinal hernias in 3.8% of 579 patients with a testicular tumour, and calculated that boys with a congenital inguinal hernia were 2.9 times more likely to develop a malignant testicular tumour.
In a series of 287 patients with a malignant testicular tumour seen in Groningen, 14 (4.8%) had been previously treated for inguinal hernia or had an inguinal hernia at the time of the orchiectomy. In this series the incidence of inguinal hernia was slightly above normal, and consequently it may be justifiable to conclude that patients with a congenital inguinal hernia, too, run a slightly increased risk to develop a malignant testicular tumour (Wobbes et al. 1980b).

II.4.2 *Atrophy*

Atrophy is another factor of possible importance in the aetiology of malignant germ cell tumours of the testis (Haines and Grabstald 1950; Hausfeld and Schrandt 1965). The mechanism of this malignant change is still obscure. Perhaps hormonal factors are of importance in this respect. On the other hand, the undescended testes are nearly always atrophic. This is why Lewis (1950) maintained that undescended and atrophic testicles have the same incidence of malignant germ cell tumours. Gilbert (1944) and Kaufman and Bruce (1963) found an increased incidence in cases of testicular atrophy resulting from mumps.

II.4.3 *Trauma*

Several patients with a malignant testicular tumour have a history which reveals a trauma of the testis involved. McKay and Sellers (1960) found this in 6.4% of their patients, while Patton et al. (1960) and Kurohara et al. (1967) reported 7%. Most authors, however, express some doubt about the significance of traumata in the aetiology of malignant testicular tumours (Patton et al. 1960; Collins and Pugh 1963). It seems more likely that the trauma draws attention to a tumour already present.
It was found in animal experiments that a single intratesticular injection of zinc chloride in fowls was followed a few months later by the development of a malignant testicular tumour (Carleton et al. 1953). It was not established with certainty whether the trauma was the true cause of the testicular tumour growth or whether the zinc chloride induced the tumour (Von Hoff 1979).

II.5 Bilateral testicular tumours

Bilateral testicular germ cell tumours are uncommon, but do occur. Hamilton and Gilbert (1942) estimated the risk of developing a contralateral malignant testicular tumour in a person with a history of a malignant testicular tumour to be 0.7%. In their series of 7000 patients, 1.6% had a bilateral tumour. In the already mentioned series of 287 Groningen patients, a bilateral testicular tumour was found in 7 cases (2.4%) (Hoekstra et al. 1981). When a second tumour of identical histology is found in the contralateral testis, the question arises whether this tumour is really a second primary tumour or a metastasis of the first. However, the second tumour nearly always becomes manifest after an interval of more than two years (Morrison et al. 1976). It has been established that the second tumour becomes manifest within five years in 50% of cases, but after as long as 20 years in 3%. The most common second germ cell tumour is the seminoma (77%), followed by tumours of the embryonal carcinoma/teratoma group (20%). Bilateral choriocarcinomas are rare (2%) (Aristizabal et al. 1978).

II.6 Familial occurrence

The occurrence of familial testicular tumours is likewise rare. The literature comprises few relevant reports. Some 30 instances have so far been described, both in brothers and in twin-brothers (Wilbur et al. 1979; Shinohara et al. 1980). Raghaven et al. (1980) found five father-and-son cases in the literature and added one of their own. Collins and Pugh (1963) found five instances of familial occurrence in a group of 974 patients with malignant testicular tumours; two of these patients were cousins, and in one of these two cases a brother was reported also to have had a testicular tumour.
Shinohara et al. (1980) recently presented a survey of 20 families in which non-twin-brothers had a malignant testicular tumour. Three families were eliminated: two because more than two members had a testicular tumour and one because the histology was unknown. In 10 of the 17 remaining families, the tumour histology was identical. In a survey of the literature on twin-brothers with a malignant testicular tumour, Wilbur et al. (1979) found the same histological type in six of the eight cases. It therefore seems as if the same type of testicular tumour can be found both in twins and in non-twins (Wobbes et al. 1981a). This contradicts Macklin's theory (1940) that a neoplasm of identical type and localization is most frequently encountered in monozygotic twins.

II.7 Extragonadal germ cell tumours

Although germ cell tumours normally develop in the testes, they can also occur at other sites in the body. Sites of predilection are the retroperitoneum, mediastinum and pineal gland. Their histology does not differ from that of malignant testicular tumours. Of course the question immediately arises whether they may not be metastases of a primary malignant testicular tumour that has regressed; and this applies in particular to retroperitoneal neoplasms. However, when detailed histological examination of the testicles reveals neither tumour tissue nor cicatricial tissue (regression of tumour tissue), the extragonadal germ cell tumour can be assumed to be a primary neoplasm (Friedman 1951; Johnson et al. 1973; Luna and Valenzuela-Tamariz 1976).

Retroperitoneally localized extragonadal germ cell tumours possibly arise from remnants of the urogenital ridge (Hansmann and Budd 1931; Mostofi and Price 1973). Mediastinal neoplasms either arise from the urogenital crest or result from an error in thymus gland development (Schlumberger 1946). Germ cell tumours of the pineal gland may arise from degenerated germ cells which, on their way from yolk-sac to gonads, may spread through the entire body, including even the head (Simson et al. 1963).

When no changes are palpable in the testicles, orchiectomy is not required as long as the extragonadal germ cell tumour fulfils the following criteria, formulated by Abell (1965): a) presence of normal germ cell tissue in the tumour capsule or its immediate vicinity; b) no metastases elsewhere; c) a high retroperitoneal localization without metastases at the lumbar or iliac level.

In order to ascertain that no tumour tissue is localized in the retroperitoneum in patients with a mediastinal tumour, a laparotomy merits serious consideration (Wobbes 1979).

CHAPTER III

METASTATIC ROUTES

III.1 Introduction

In patients presenting for the first time with a non-seminomatous tumour of the testis, metastases are frequently demonstrable. The percentages reported in the literature range from 14 to 39 (Patton et al. 1960; Thompson et al. 1961; Johnson 1976). Since metastases are sometimes not demonstrable at clinical and radiological examination but are found at operative staging, these percentages are too small. Vugrin et al. (1979) found only local lesions (stage I) in 44% of 1850 patients with a non-seminomatous tumour; metastases in regional lymph nodes (stage II) were found in 23%, and distant metastases (stage III) were already present in 33% of the patients.

The metastatic pattern of testicular tumours does not differ in principle from that of other neoplasms. Apart from direct extension to adjacent tissues, e.g. rete testis, epididymis and spermatic cord, tumour tissue can be transported by lymph or blood. Haematogenous metastasis can take place in two different ways: direct tumour invasion of the blood vessels, or invasion first of the lymphatic vessels and then, via thoracic duct and cisterna chyli, in the subclavian vein. As a rule, however, malignant testicular tumours metastasize primarily by the lymphatic route. An exception to this rule are choriocarcinomas, which are notorious for their direct haematogenous dissemination (Patton et al. 1960; Borski 1973).

Because lymphogenous metastasis is so important for staging and treatment, it will be discussed in some detail. The literature on the lymph drainage system of the testes will first be reviewed. Next, the results of some important clinical studies of lymphogenous metastasis will be summarized.

III.2 The lymph drainage system of the testis

The lymph drainage system of the testis differs from that of other organs. This is intimately related to the embryonic development of the testis. Until the tenth week after conception, the primordium of the sexual glands - the urogenital ridge - is localized in an area which extends from C6 to S2. Subsequently, an absolute and relative descent of the primordium of the testicles occurs. The latter results from the more rapid development of the cranial part of the body (Gray and Skandalakis 1972). The testes pass through the inguinal canal in the eighth month. In this process of descending to the scrotum, the testicles take the blood vessels and lymphatic vessels along, so to speak, but the lymph nodes remain behind. Consequently the primary lymph node sites are at the lumbar level: at the level of L1 - L3 on the right, and at L1 - L2 on the left side.

At the turn of the century Most (1899), Cuneo (1901) and Jamieson and Dobson (1910) published detailed descriptions of the lymph drainage system of the testes on the basis of cadaver studies. The review of these findings presented by Rouvière (1932) in the manual „Anatomie des Lymphatiques de l'Homme" can be summarized as follows.

Lymphatic capillaries form a network around the seminiferous tubules. Via the septa they extend to a network in the tunica albuginea. This second network comes together at a level craniodorsal to the testis, from which level four to eight lymphatic vessels arise which extend to the spermatic cord. These lymphatics accompany the spermatic artery and vein, cross the ureter, ramify and curve away to the lymph nodes. The connections with the retroperitoneal lymph nodes on the right differ from those on the left.

On the right, the lymphatics extend to the nodes localized in the area between the renal vein and the bifurcation of the aorta. Two or three trunks terminate in two or three precaval nodes. The most caudal node at the level of the aortic bifurcation receives one trunk. The pre-aortic nodes likewise receive one or two trunks. Jamieson and Dobson (1910) reported that, in one out of ten cases, one trunk ends in a node localized in the angle between inferior vena cava and right renal vein.

On the left, the lymphatics extend in two-thirds of cases to nodes localized lateral to the aorta and caudal to the renal vascular pedicle. In the remaining one-third of cases they terminate likewise in pre-aortic nodes. According to Rouvière there is, in addition to the above mentioned pathways, an accessory route which ends in a node localized ventral to the external iliac vein, at the point where it is crossed by the ureter. Lymphatics originating from the

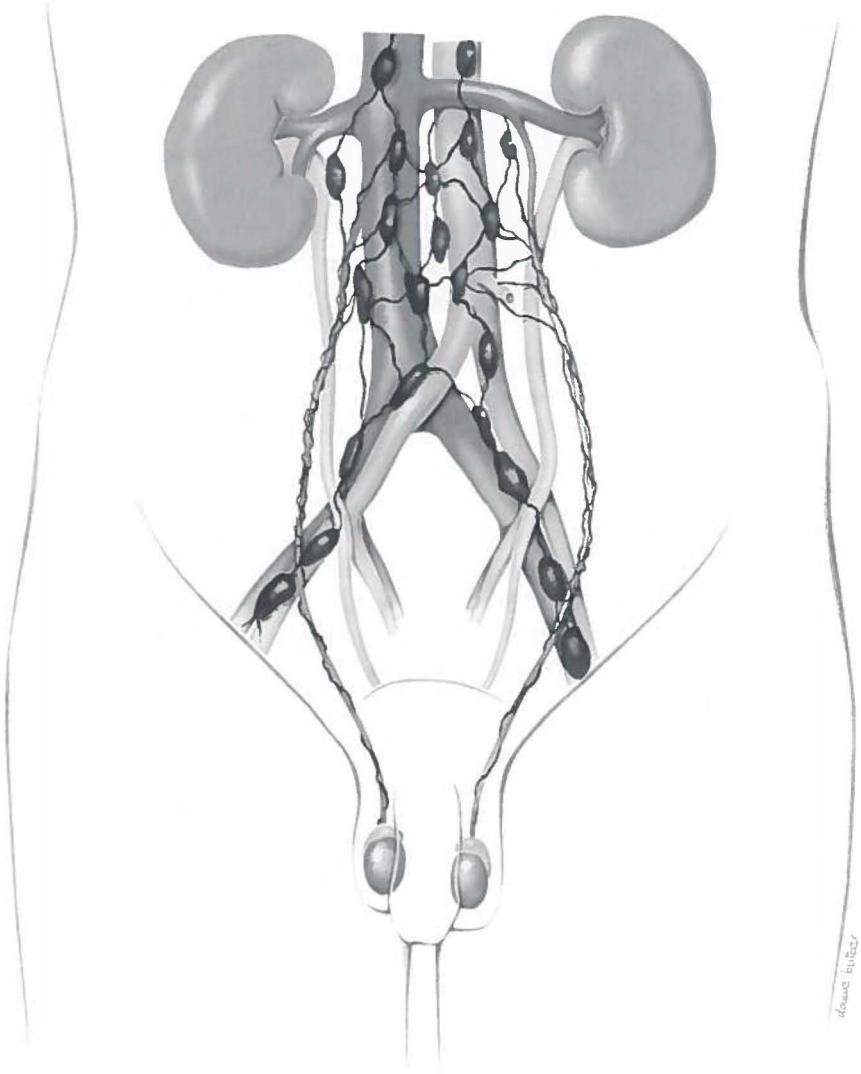


Fig. III.1 Anatomy of the lymph drainage system of the testis.

epididymis terminate in the same area. Moreover, interconnections might well exist.

III.3 Funicular lymphography

The direct lymph drainage system of the testis can be visualized by lymphography (Busch and Sayegh 1963; Sayegh et al. 1966; Hultén et al. 1973). However, this procedure can only be carried out before orchiectomy. For this purpose a lymphatic vessel in the spermatic cord must be traced after injection of a few millilitres of methylene blue into the testis. After cannulation, the contrast medium is infused in the same way as in pedal lymphography. The first nodes to fill are the primary lymph nodes of the testis. Chiappa et al. (1966) used the designation "specific testicular lymph centre" in this context.

The combination of traditional pedal lymphography with funicular lymphography shows that, in the former, not all sentinel nodes fill. These sentinel nodes are localized immediately lateral to the left and right paralumbar lymph node sites visualized in pedal lymphography.

These lymphographic studies demonstrated that no primary lymph nodes of the testis are to be found at the iliac level, as earlier investigators maintained (Busch and Sayegh 1963; Chavez 1967; Hultén et al. 1973). They also revealed that there are lymphatic connections between the right and the left side (cross-over). Hultén et al. (1973) in fact observed right-to-left cross-over in 50% of cases. It is worthy of note that left-to-right cross-over is hardly observed. It is found almost exclusively when the lymph nodes are completely occupied by tumour tissue (retrograde filling) (Hultén et al. 1973; Storm et al. 1977).

Although the so-called primary lymph centre of the testis is generally localized at the level of the lumbar vertebrae, Chiappa et al. (1966) and other authors before them (Busch and Sayegh 1963; Busch et al. 1965) reported that at funicular lymphography they had found contrastmedium filled nodes also at the level of T11 in a few cases. Apart from the low thoracic lymph nodes, mediastinal lymph nodes sometimes filled at the same time as the thoracic duct. In a study of this kind, Hultén et al. (1973) also observed filling of supraclavicular lymph nodes, at least if the retroperitoneal lymph nodes contained no metastases.

III.4 Clinical observations

Are the classical anatomical descriptions of the testicular lymph drainage

system and the later lymphographic findings in agreement with clinical findings? As regards cross-over, Fein and Taber (1969), Hultén et al. (1973) and Storm et al. (1977) found abnormal nodes on the contralateral side in 27, 44 and 30% of cases, respectively. These authors, however, simply distinguished between ipsilateral and contralateral without clearly defining these regions.

A more detailed study was performed by Ray et al. (1974), who subdivided the right ipsilateral region into paracaval, precaval, interaortocaval and pre-aortic areas. They defined the iliac region as the region encompassing the common iliac artery and the right external iliac artery. The left ipsilateral region was subdivided into para-aortic and pre-aortic areas, and the region around the common iliac artery and left external iliac artery was defined as para-iliac.

Ray et al. (1974) found ipsilateral metastases in 85%, ipsilateral and contralateral metastases in 13% and solely contralateral metastases in only 1.6% of 160 patients with a right-sided primary tumour. In 122 patients with tumours of the left testicle, they found ipsilateral lymph node metastases in 80% and bilateral metastases in 20%. Notably, paracaval or para-aortic solitary metastases were never found either on the right or on the left. A solitary lymph node metastasis was found along the common iliac artery in two and along the external iliac artery in one of 18 patients with a right-sided tumour and a solitary lymph node metastasis. In a group of 17 patients with a left-sided tumour and a solitary lymph node metastasis, the corresponding numbers were four and one.

Unlike Ray et al. (1974), Hultén et al. (1973) never found solitary iliac metastases as long as the lumbar lymph nodes contained no metastases. Moreover, these findings reported by Ray et al. (1974) contradict observations made by funicular lymphography (Busch and Sayegh 1963).

In view of their findings, Ray et al. (1974) did not support the theory of the so-called specific testicular lymph centre advanced by Chiappa et al. (1966). Nor did their findings correspond with those reported by Fein and Taber (1969), Hultén et al. (1973) and Storm et al. (1977), who all found a far larger percentage of contralateral lymph node metastases.

The differences may be explained by one or several of the following factors: Ray et al. (1974) performed bilateral dissection in only 44% of the cases; the pre-aortic area has been included in the right as well as in the left ipsilateral region; in the case of a delay, metastasis to the contralateral side is bound to increase; there are no data on the local primary tumour extent or on previous

operations in the inguinal region (III.5), but metastasis to the para-iliac lymph nodes can be expected when the tumour invades the epididymis, and abnormal metastasis has been described after inguinal operations.
That solitary metastases can also be found cranial to the renal vascular pedicle was demonstrated in the study by Donohue et al. (1979), who located a solitary lymph node metastasis above the left renal artery in one patient in a group of 28. In another group of 28 patients, seven had lymph node metastases cranial as well as caudal to the renal vascular pedicle. It is also conceivable that a testicular tumour may produce solitary metastases in supraclavicular lymph nodes. Donohue et al. (1977) described this in one of a group of 39 patients. It is to be noted in this context that metastases had not been demonstrable elsewhere on the basis of clinical findings alone. Retroperitoneal lymph node dissection had not been performed.
Buck et al. (1972) never found histologically positive supraclavicular lymph nodes in the absence of demonstrable metastases elsewhere. When there were indications of retroperitoneal lymph node metastases in the absence of metastases elsewhere, however, they found supraclavicular lymph node metastases in four patients in a group of 25 (16%). Donohue et al. (1977) reported the same findings in three patients in a similar group of 14 (21%).

It can be stated in summary that there are some discrepancies between actually observed lymphogenous metastasis of malignant testicular tumours and the classical description of the lymph drainage system of the testes. The metastatic pattern is more erratic than might be expected on theoretical grounds. A factor of possible importance in this respect is the local extent of the primary tumour, which may open up other metastatic routes.

III.5 Abnormal metastatic pattern after an operation in the inguinal region

As already pointed out in subsection II.4.1, patients with an undescended testicle have an increased risk of malignant testicular tumour development. Orchiopexy, if performed, exerts an influence on the manner of metastasis, for lymphatics in the spermatic cord may be damaged in this operation. In that case new connections are formed, in particular with the inguinal lymph nodes. A similar change in the lymph drainage system can also occur after other operations in the inguinal region, e.g. for inguinal hernia or testicular hydrocele. The literature presents no data on the incidence of metastasis to inguinal lymph nodes after orchiopexy. Witus et al. (1959) and Herr et al.

(1973) described two and four cases, respectively, without specifying the size of the entire group of patients studied.
In the Groningen series, inguinal lymph node metastases were found in four patients in a group of 12 who had undergone orchiopexy (Wobbes et al. 1980b). In one patient in a group of 14 with a testicular tumour after an operation for inguinal hernia, both inguinal and para-iliac lymph node metastases were found.

III.6 **Haematogenous metastasis**

Metastases are found at the first examination in about one-third of patients with a malignant testicular tumour (Vugrin et al. 1979). As already mentioned in section III.1, haematogenous metastasis can take place in two ways: directly or via lymphatics and the thoracic duct.
Brain metastases are found in about 25% of postmortems on patients with a testicular tumour (Vugrin et al. 1979). It has been established that these cerebral metastases are preceded or accompanied by pulmonary metastases. This is understandable in view of the fact that tumour cells transported in the blood first pass through the pulmonary and then, after passing the left heart, through the systemic circulation. Choriocarcinomas, embryonal carcinomas and tumours combined with embryonal carcinoma metastazise particularly to the brain. In advanced stages of the disease, metastases can also be found in the liver and the skeleton.

CHAPTER IV

METHODS OF INVESTIGATION

IV.1 Introduction

The investigation to which a patient with a malignant testicular tumour is submitted, is aimed at determination of the extent of the tumour growth. Especially the retroperitoneum and the lungs are important in this respect. One should always bear in mind that the accuracy of this investigation has its limitations. In all cases there is a varying discrepancy between clinical observations on the one hand, and peroperative or postoperative findings on the other. In spite of various sophisticated new diagnostic procedures such as lymphography, CT-scan, echography and tumour marker assay, the current inaccuracy is about 20% (Fraley et al. 1980). The discrepancies are to be ascribed largely to microscopic and minimal metastases in the retroperitoneal lymph nodes.

This chapter presents a survey of diagnostic procedures currently in use in tumour staging after a diagnosis of malignant testicular tumour. These procedures focus on retroperitoneum and lungs, because these areas are the sites of predilection for metastases of malignant testicular tumours.

IV.2 Physical examination

IV.2.1 *Primary tumour*

The patient usually presents with a painless swelling, sometimes associated with a sensation of heaviness. In many cases a trauma focuses attention on the swelling. In 4-14% of cases the metastases produce the first symptoms of the disease, whereas the primary tumour is still unnoticed (Johnson 1976). The diagnosis "malignant testicular tumour" is frequently overlooked. In a series of 100 patients, Hill (1978) found a significant delay due to

erroneous diagnosis in 37 cases. Confusion with epididymo-orchitis was the most frequent error. In 1968, Hill reported the striking fact that admixture of infantile embryonal carcinoma and poorly differentiated cells was a frequent finding in patients in whom the diagnosis had been initially missed. Post and Belis (1980) found a delay in excess of three months in as many as 50% of the cases. In their series of patients, this had an unmistakably unfavourable effect on the prognosis: while the 3-year survival was 81% in patients in whom the proper diagnosis had been established within three months, it was only 60% in patients whose tumour had been diagnosed later. Any testicular enlargement, therefore, calls for a detailed investigation. The rule that every testicular tumour should be regarded as malignant until proven to be otherwise, remains valid.

IV.2.2 *Lesions found in association with malignant testicular tumours*

Physical examination is of course the first step in the diagnosis of metastases of a malignant testicular tumour. This examination should be made at the mere suspicion of such a tumour. The abdomen should be examined first. Large retroperitoneal lymph node metastases are as a rule palpable (extensive retroperitoneal metastasis). In patients with a history of orchiopexy or an operation for inguinal hernia or testicular hydrocele, the inguinal regions should be examined for metastases. We know that, as a result of the change in lymph drainage, it is here that the primary lymph node sites are now localized (Wobbes et al. 1980a, b).

The supraclavicular region is the lymph node site most likely to reveal palpable changes, especially in the case of advanced dissemination. Donohue et al. (1977) found supraclavicular metastases at physical examination in three out of 57 patients (5%), and a supraclavicular lymph node biopsy revealed metastases in two more patients.

The presence or absence of gynaecomastia merits special attention. The enlargement is often bilateral and develops in response to hormones produced by the tumour. Gynaecomastia is particularly observed when the tumour contains trophoblastic tissue, but develops also in association with a seminoma (Smithers 1976). Yet gynaecomastia is not a frequent finding. Bradfield et al. (1973) found it in 2.5% of patients and Fergusson (1963) reported 2.6%. Like other types of secondary gynaecomastia, it usually shows regression when the tumour and the metastases are treated (Wobbes 1980).

IV.3 **Radiological examination**

Several methods are available for radiological staging of a malignant testicular tumour. Lymphography of the retroperitoneal lymph nodes and, more recently, the CT-scan are of special importance. Other radiological methods are intravenous urography, aortagraphy and cavography. Tomography of the lungs is employed to locate lung metastases. In recent years the CT-scan technique has seemed to make it possible to trace even very small metastases.

IV.3.1 *Lymphography*

Since the first report on pedal lymphography by Kinmonth in 1952, this method has been used also to trace lesions of retroperitoneal lymph nodes. It was not until the early Sixties that lymphography was employed in the diagnosis of malignant testicular tumours. Wallace et al. (1961) were the first to mention the possibility of this application in this group of tumours. The radiological features visualized by bipedal lymphography are not specific for testicular tumours. In many cases, however, the features and the localization of the lesions permit a conclusion about the presence or absence of retroperitoneal metastases. The technique of lymphography is presumed to be known and need not be discussed here.

The principal anomalies found in the presence of metastases are filling defects and lymph node enlargement. Other abnormal patterns are: displacement of lymph node sites beyond the line connecting the transverse processes, stasis, collaterals, lymphovenous anastomoses and absence of lymph nodes or groups of lymph nodes (Maier and Schamber 1972; Jackson 1974). Jackson (1974) demonstrated that lymphography has its limitations precisely in the case of testicular tumours. He discovered that only 25% of the lymph nodes up to level L1 filled on the right, versus 50% on the left. The practical significance of this finding lies in the fact that non-filling of nodes in the high lumbar areas - particularly on the right - does not necessarily indicate metastasis. But it also implies that metastases at high lumbar levels are in many cases not demonstrable lymphographically.

Another limitation of lymphography in the diagnosis of metastases of malignant testicular tumours lies in the fact that the so-called specific testicular lymph centre - i.e. the nodes to which the tumor metastasizes primarily - is localized immediately lateral to the nodes that fill in pedal lymphography (Cook et al. 1965; Chiappa et al. 1966). This has already been

discussed in some detail in section III.3. Radiological visualization of these sentinel nodes would require funicular lymphography, but this can be performed only prior to orchiectomy. In the major centres, however, most patients present after the diagnosis has been made elsewhere by means of orchiectomy. Moreover, funicular lymphography is a time-consuming procedure which markedly increases the operation time. Another possible disadvantage of this method is that injection of dyes and contrast media may cause dissemination of tumour cells.
However, the reliability of this form of lymphography is high. Hultén et al. (1973) found 100% correlation with the histology of the ipsilateral lymph nodes, versus only 67% for the contralateral nodes. Although funicular lymphography may on theoretical and clinical grounds be described as the method par excellence for radiological visualization of lymph node metastases, therefore, its use has been limited for practical reasons.

The fairly high reliability of funicular lymphography contrasts with the less high reliability of pedal lymphography, for which the literature reports values ranging from 62% to 89% (see table IV.1) for correlations with operative and/or histological findings. It made no difference whether the lymphogram was correlated prospectively or retrospectively (Kademian and Wirtanen 1977). It was established that a lymphogram is most reliable if interpreted as positive, in which case Fein and Taber (1969) found 100% correlation. On the other hand, Storm et al. (1977) found only 59% correlation.

Authors	Number of lymphograms with correlation	Reliability if positive		negative		Overall reliability	
Fein & Taber (1969)	50	20/20	100%	20/20	66%	40/50	80%
Wallace & Jing (1970)	67	17/18	94%	41/49	84%	58/67	87%
Maier & Schamber (1972)	59	32/35	91%	18/24	75%	50/59	85%
Hultén et al. (1973)	39	21/23	91%	12/16	75%	33/39	85%
Jonsson et al. (1973)	19	11/12	92%	8/10	80%	19/22	86%
Safer et al. (1975)	33	8/12	67%	18/21	86%	26/33	79%
Kademian & Wirtanen (1977)	45	28/29	97%	12/16	75%	40/45	89%
Zaunbrunner et al. (1977)	33	7/8	97.5%	18/25	72%	25/33	76%
Storm et al. (1977)	45	10/17	59%	18/28	62%	28/45	62%

Table IV.1: Lymphographic reliability correlated to histological or operative findings.

The reliability of lymphograms interpreted as normal, however, is far less high. False negative interpretations are made in 62-86% of cases. Lymphographic demonstration of actually existing metastases is even less reliable; values reported in the literature range from 50% to 87% (see table IV.2).

Authors	Positive histology Positive lymphography	Percentage
Fein & Taber (1969)	20/30	64%
Wallace & Jing (1970)	17/25	68%
Maier & Schamber (1972)	32/38	84%
Hultén et al. (1973)	21/25	84%
Jonsson et al. (1973)	10/12	83%
Safer et al. (1975)	8/12	66%
Kademian & Wirtanen (1977)	28/32	87%
Zaunbrunner et al. (1977)	7/14	50%
Storm et al. (1977)	10/20	50%

Table IV.2: Lymphographic reliability in the presence of retroperitoneal metastases.

The relatively large percentage of false negative findings is partly inherent to the method (as explained above), and partly results from the presence of micrometastases. Maier (1979) found micrometastases in six out 24 patients whose readily interpretable lymphograms had been accepted as normal. Fein and Taber (1969) maintain that metastases with a diameter of less than 2 cm are not radiologically demonstrable.
The most reliable criterion in interpretation of lymphograms has not yet been defined. Storm et al. (1977) attached most importance to enlarged lymph nodes and filling defects in the margin of the lymph node, while Loening et al. (1977) described obstruction of the lympahtic vessels as the most reliable criterion.

If lymphography is of only limited value in the diagnosis of non-seminomatous tumours of the testis, then the question arises whether it should be performed at all. For advocates of retroperitoneal lymph node dissection as method of staging and treatment, lymphographic findings make no difference in treatment. To them, in other words, lymphography is of no consequence. Of course the same applies to other methods of investigation which focus on the retroperitoneum. Extensive retroperitoneal metastases can just as well be demonstrated by careful palpation or with the aid of intravenous urography. Should the retroperitoneal metastases be small, retroperitoneal lymph node dissection is nevertheless performed.

Kagan and Skinner (1978) reported that, in the context of health care economizing, this type of examination is therefore no longer carried out. Moreover, they noted an inflammatory reaction around the lymph nodes, caused by oil in the contrast medium. This would only further impede lymph node dissection.
Advocates of radiotherapy (without laparotomy) as sole method of choice in the treatment of metastases of a malignant non-seminomatous tumour of the testis, however, need lymphography as a staging procedure (currently supplemented by CT-scan). In order to be able to compare results of radiotherapy with those of operative therapy - in an attempt to establish which of the two is ultimately to be preferred - lymphography is still needed in both groups.
Another reason for performing lymphography is that a plain X-ray of the abdomen after dissection can establish whether all lymph nodes containing contrast medium have in fact been removed. Consequently it seems that pedal lymphography need not be discontinued as yet, even though its value is only relative.

IV.3.2 *CT-scan*

Although the patients of this study were not routinely examined with the CT-scanner, this new diagnostic procedure is nevertheless briefly discussed. Few publication have so far reported on the reliability of this method in the diagnosis of testicular tumours. Kuster and Imhof (1979) found a reliability of 85% in 13 examinations correlated to the findings at operation and postmortem examination. Lee et al. (1979) reported 90% reliability when correlating the CT-scan findings partly with histological and partly with lymphographic and follow-up findings.
The available literature would seem to warrant the conclusion that the CT-scan is more reliable than lymphography. Yet the former cannot replace the latter, which has theoretical advantages. The CT-scan cannot distinguish changes within the lymph node because node enlargement is the only criterion. Consequently, small metastases can be easily overlooked (Lee et al. 1979; Husband et al. 1979). On the other hand, the CT-scan can supply much more information on the cranial lumbar areas, which are nearly inaccessible to pedal lymphography (Fraley et al. 1980). It can be safely stated for the time being that CT-scan and lymphography are procedures which supplement each other.

IV.3.3 *Intravenous urography*

Intravenous urography is a routine procedure in our department whenever a malignant testicular tumour has been diagnosed. In the case of extensive retroperitoneal metastases, the tumour mass can displace or obstruct the ureters. It is our custom to perform this procedure together with lymphography in order to achieve a good overview of the retroperitoneum. This procedure also supplies information on possible anatomical anomalies of the urinary drainage system (horse-shoe kidneys, duplication of ureters, etc.) and thus eliminates unpleasant surprises during retroperitoneal lymph node dissection.

IV.3.4 *Aortography / cavography*

Angiography of retroperitoneal blood vessels is not routinely performed as a rule. Yet this type of investigation can be supplemental in the diagnosis of retroperitoneal metastases. Particularly if more information is required on cranial lumbar areas (often not visualized in lymphography), cavography or phlebography of the renal or spermatic veins can sometimes be very useful (Lien and Kolbenstved 1977).

In patients with large retroperitoneal metastases, aortography and cavography may be indicated for preoperative information on displacement or obstruction of these vessels. Precisely in these cases it is sometimes necessary to sacrifice the inferior vena cava or to replace segments of the abdominal aorta (Skinner 1977).

IV.4 Echography

Echography of the retroperitoneum is not yet widely performed. Yet this procedure can give supplemental information in the diagnosis of large retroperitoneal metastases. The size of the metastases can be echographically determined; and the degree of regression and progression can be determined by regularly repeated echography in the course of treatment. One major advantage of this procedure is that it hardly inconveniences the patient (Tyrrell et al. 1977).

For small lymph node metastases, however, the procedure is less suitable. Fraley et al. (1980) found 82% correlation with histological findings. False negative observations were found in particular in patients with microscopic metastases and only slight node enlargement. For the area around the vascular pedicle, echography proved to be more reliable than lymphography.

IV.5 Radiological examination of the lungs

After the retroperitoneal lymph nodes, the lungs are the organs to which malignant testicular tumours are most likely to metastasize. Some 85-90% of all metastases are demonstrable by anteroposterior and lateral chest X-rays, and this type of examination is therefore not good enough for staging.

In our department, pulmonary tomography is routinely carried out when a malignant testicular tumour has been diagnosed. In this way, lesions up to 1 cm in diameter can be diagnosed. Even smaller lesions can be diagnosed since the introduction of the CT-scan, but this procedure has the disadvantage that more benign lesions are also detected, and sometimes interpreted as metastases (Fraley et al. 1980).

IV.6 Supraclavicular lymph node biopsy

As already explained in this chapter, metastases in the supraclavicular lymph nodes can in some cases be found at physical examination. A study published by Buck et al. (1972) shows, however, that one should not rely exclusively on palpatory findings. These authors found metastases in an elective supraclavicular lymph node biopsy specimen in three out of 25 patients (13%) in stage II.

A study by Donohue et al. (1977a) showed that lymphographic data on the supraclavicular lymph nodes do not always correlate with histological data. They found false negative lymphograms in 11.2% and false positive lymphograms in 8.8% of cases. Both Buck et al. (1972) and Donohue et al (1977a) therefore recommend supraclavicular lymph node biopsy in all patients, regardless of the stage of the disease.

In our department, however, this procedure is not routinely performed. Supraclavicular lymph node biopsy is done when lymphographic findings are abnormal, when lymph node metastases are palpable in the retroperitoneum, or when laparotomy reveals lymph node metastases. These biopsies are performed solely for the purpose of staging. A survey of the literature by Fowler et al. (1979) disclosed that supraclavicular lymph node metastases were found in biopsy specimens from 9% of patients in clinical stage II, although palpation had failed to reveal them. In this study, the chance of finding a supraclavicular metastasis in stage I was found to be 1.5%. It should be noted, however, that this stage I had been determined solely by clinical examination and not by means of a retroperitoneal lymph node dissection.

There are no reports in the literature on solitary metastases in supraclavicular lymph nodes, and on theoretical grounds their occurrence must be regarded as unlikely.

IV.7 Tumour markers

It has been established in recent years that testicular germ cell tumours are associated in many cases with increased concentrations of ß-human chorionic gonadotropin (HCG) and α-foetoprotein (AFP) in the serum. Particularly the introduction of the sensitive radio-immuno-assay has made it possible to demonstrate even minimal concentrations of these tumour markers in serum (Waldman and McIntire 1972). This has distinctly changed the treatment of testicular germ cell tumours.
The role currently played by these two substances in the diagnosis and treatment of malignant testicular tumours is outlined in the following subsections.

IV.7.1 *ß-Human chorionic gonadotropin (HCG)*

HCG is a glycoprotein normally produced in the syncytiothrophoblast cells of the placenta. It is structurally related to luteinizing hormone (LH) and follicle-stimulating hormone (FSH). They have identical α-chains but their ß-chains differ in such a way that an antigen-antibody reaction aimed at the ß-chain is specific. The serum HCG concentration can in this way be measured very accurately (Narayana et al. 1979). The far less sensitive Ascheim-Zondek reaction formerly used to demonstrate HCG in urine, has been completely abandoned. Serum levels exceeding 2 ng/ml are regarded as abnormal. With the aid of the immuno-peroxidase technique it was demonstrated that HCG is in fact localized in the syncytiotrophoblast cells. A study by Kurman et al. (1977) showed that choriocarcinoma is associated with an increased serum HCG concentration in 100% of cases; the corresponding values for embryonal carcinoma and endodermal sinus tumour are 80% and 25%, respectively. The same authors did not find an increased serum HCG concentration in patients with a teratoma, but in 14% of the patients with a seminoma they did. Javadpour et al. (1978) found an increased serum HCG level in 5% of their patients with a seminoma. At painstakingly careful histological examination, however, they found choriocarcinoma cells as well in one case. Lange et al. (1976) likewise found histological evidence of non-seminomatous component in two patients with a

seminoma and with an increased HCG level. Cases of seminoma with increased HCG level should therefore always be studied with great care.
Some 40% of the non-seminomatous tumours are combinations of several cell types; the remaining 60% are pure types. HCG is found to be present in 77-89% of cases in the group of the non-seminomatous tumours (Newlands et al. 1976; Scardino et al. 1977).

IV.7.2 *α-Foetoprotein (AFP)*

AFP is an α_1-globulin which is present in human foetal serum in the 12th-15th week. Very low concentrations are still demonstrable during the first few weeks after birth.
In 1963, Abelev et al. found an increased serum AFP level in mice with a hepatoma; this protein can be identified also in 40-80% of human hepatoma cases (Alpert et al. 1968). Later it was found that AFP is frequently demonstrable also in serum from patients with a testicular tumour. The radioimmuno-assay method makes it possible to demonstrate concentrations as low as 5 ng/ml. Serum levels in excess of 16 ng/ml are abnormal (Waldman and McIntire 1972).
It has been reported that AFP is not found in seminoma, teratoma and choriocarcinoma cases (Kohn et al. 1976; Newlands et al. 1976; Kurman et al. 1977; Narayana et al. 1978; Javadpour 1978). However, there are a few reports on increased AFP levels in patients with a seminoma, Kohn et al. (1976) mentioning the possibility of admixture of non-seminomatous components.
The neoplasm most active in producing AFP is the endodermal sinus tumour (yolk-sac tumour, infantile embryonal carcinoma) (Teilum et al. 1975; Kurman et al. 1977). These tumours develop mostly in childhood and sporadically in adults. Kurman et al. (1977) found increased AFP levels in 11 of 15 cases of adult embryonal carcinoma; in seven of these cases AFP was demonstrable in tumour cells by histopathological techniques.
Newlands et al. (1976) found increased AFP levels in 86% of 39 patients with a non-seminomatous tumour; Kohn et al. (1976) reported this in 61% of 88 patients, and Scardino et al. (1977) in 58% of 36 patients.

IV.7.3 *The clinical value of HCG and AFP assays*

Determination of HCG and AFP levels is of value in the diagnosis of non-seminomatous tumours because both substances occur in association with several types of testicular tumours.

Several groups of investigators found both markers increased in 80-90% of cases (Waldman and McIntire 1974; Newlands et al. 1976; Scardino et al. 1977; Bosl et al. 1981). They found no false positive but in some cases false negative results. Scardino et al. (1977) found lymph node metastases but no increased tumour marker levels in four out of 20 patients, in three of whom the metastases proved to be only microscopically demonstrable. They also reported that the majority of stage I patients showed no increased tumour marker levels even before orchiectomy.

Because fals negative tumour marker assays are always possible, the treatment of non-seminomatous tumours of the testis should not be based exclusively on these assays. A testicular tumour with negative markers is not always a benign tumour, and a normal lymphogram with negative markers does not necessarily imply stage I. Tumour markers have proved to be of value as a source of supplemental information, but the results are not always conclusive. Orchiectomy continues to be required for a final diagnosis; and laparotomy or retroperitoneal lymph node dissection remains the only reliable staging procedure (Moore et al. 1978).

Tumour marker assays are of great value in evaluation of the effect of chemotherapy. It is of importance always to determine both HCG and AFP levels, because there are reports on a few instances of so-called discordance (one of the markers decreasing to normal values in response to therapy, whereas the other remains increased (Braunstein et al. 1973)).

The half-life of both markers should also be taken into account. This is 16 hours for HCG and 5 days for AFP. At least two determinations should be made - at an interval of a few days - in order to establish the effect of therapy.

Apart from their importance in diagnosis and evaluation of therapeutic effects, tumour markers have proved to be useful in tracing recurrence. Even before other diagnostic methods reveal a recurrence, slightly increased tumour marker levels can already indicate it (Scardino et al. 1977; Willemse et al. 1981).

It can be concluded that tumour markers are an important source of supplemental information for evaluation of patients with a non-seminomatous tumour of the testis. A positive result implies the presence of vital tumour tissue, but a negative result does not exclude it.

CHAPTER V

CLASSIFICATION AND STAGING

V.1 Introduction

This chapter first presents a survey of histological classifications of malignant testicular tumours. A review of the literature focuses on the histology and origin of germ cell tumours, because these are of importance for treatment and prognosis. Secondly, problems in the staging of testicular malignancies are discussed in some detail.

V.2 Histological classifications

There is no consensus about the histological classification of testicular tumours. In 1946, Nesbit and Lynn wrote: "For the clinician, chaos is the only word which adequately describes the present conflict of opinion regarding the pathology of testicular neoplasms". Two theories had prevailed until that time: that advocated by Ewing and supporters (1911), who regarded all testicular tumours as being of teratoid origin, and that advocated by Chevassu and supporters (1906), who considered seminomas to be a separate type of tumour.

Even today there is no agreement about histological classification. There is no classification that accounts for the differences in views on histogenesis and at the same time is of use to the clinician for decisions regarding therapy. Since 1946, however, there have been important developments which have finally led to a number of classifications that roughly correspond with each other. In 1946, Friedman and Moore published a classification on a distinctly histological basis. After analysing 922 testicular tumours, they designed a classification based on four histological patterns which covered 96% of all testicular tumours. They distinguished: 1) seminomas, 2) embryonal carcinomas, 2a) chorioepitheliomas, 3) teratomas, and 4) teratocarcinomas.

Chorioepitheliomas were regarded as a subgroup of embryonal carcinomas. A few years later Dixon and Moore (1953) published a clinical/pathological study of data on 990 testicular tumours. Of these tumours, 96.5% proved to originate from germ cells, while 3.5% were of different origin. The germ cell tumours were found to comprise the following tumours or tumour combinations: 1) seminomas, 2) embryonal carcinomas, 3) teratomas and 4) choriocarcinomas (table V.1). On the basis of biological behaviour and morphogenesis, they divided these tumours into five groups. The classification of Dixon and Moore (1953) is in actual fact not a histological classification, but rather one based on clinical tumour behaviour.

In 1973, Mostofi and Price of the American Armed Forces Institute of Pathology (AFIP) published a new classification which - like that suggested by Friedman and Moore (1946) - was based on histology. They distinguished germ cell tumours with a single cell type - seminomas, embryonal carcinomas, teratomas and choriocarcinomas - and germ cell tumours with several cell types (table V.1).

In the context of the standardization of histological tumour classifications, the World Health Organization (WHO) almost simultaneously suggested a classification which differed from that of Mostofi and Price (1973) only in details (Mostofi and Sobin 1977). The recommendation was, always to specify the separate cell types of tumours presenting more than one histological pattern. The term teratocarcinoma was reserved for combinations of embryonal carcinoma and teratoma.

Apart from these American classifications there is a British classification designed by the British Testicular Tumour Panel (Collins and Pugh 1964). It divides the tumours into teratomas and seminomas. The teratomas are subdivided according to the degree of differentiation, the extremes being Teratoma Differentiated (TD) and Malignant Teratoma Anaplastic (MTA). Intermediate forms between the well-differentiated and the anaplastic tumours are Malignant Teratoma Intermediate A (MTIA) and Malignant Teratoma Intermediate B (MTIB). Tumours containing trophoblast components are referred to as Malignant Teratoma Trophoblastic (MTT).

In 1976 the British Testicular Tumour Panel slightly modified this classification because there proved to be no difference in clinical behaviour between MTA and MTIB (Pugh and Cameron 1976); these two categories are now known collectively as Malignant Teratoma Undifferentiated (MTU). The term MTIA has been rejected and replaced by Malignant Teratoma Intermediate (MTI). This modified version by the British

Dixon & Moore (1953)	Collins & Pugh (1964)	British Testicular Tumour Panel (Pugh & Cameron 1976)	Mostofi & Price (1973)	WHO (Mostofi & Sobin 1977)
pure seminoma (I)	seminoma classical spermatocytic malignant teratoma anaplastic (MTA)	seminoma classical spermatocytic	seminoma typical spermatocytic anaplastic	seminoma typical spermatocytic anaplastic
embryonal carcinoma ± seminoma (II)	malignant teratoma, intermediate, with no differentiated or organoid elements (MTIB)	malignant teratoma, undifferentiated (MTU)	embryonal carcinoma adult polyembryoma	embryonal carcinoma
teratoma with embryonal carcinoma and/or choriocarcinoma ± seminoma (IV)	malignant teratoma intermediate, with organoid elements (MTIA)	malignant teratoma, intermediate (MTI)	embryonal carcinoma with teratoma ("teratocarcinoma")	embryonal carcinoma with teratoma ("teratocarcinoma")
teratoma, ± seminoma (III)	teratoma differentiated (TD)	teratoma differentiated (TD)	teratoma mature immature	teratoma mature immature
choriocarcinoma ± embryonal carcinoma and/or seminoma (IV)	malignant teratoma trophoblastic (MTT)	malignant teratoma trophoblastic (MTT)	choriocarcinoma	choriocarcinoma
	orchioblastoma	yolk sac tumour	embryonal carcinoma, infantile (juvenile)	yolk sac tumour

Table V.1: Comparison of the most important classifications of germ cell tumours of the testis (slightly modified from: Nochomovitz et al. 1977).

Testicular Tumour Panel corresponds roughly with the classification published by Dixon and Moore (1953), but less with that of the WHO (Mostofi 1980).
The literature shows that the classifications of Friedman and Moore (1946), Dixon and Moore (1953) and the British Testicular Tumour Panel (Collins and Pugh 1964; Pugh and Cameron 1976) are widely used. The WHO classification has as yet found only limited acceptance, possibly because it is too detailed and therefore inconvenient in clinical practice.
As pointed out, the classifications of Dixon and Moore (1946), Collins and Pugh (1964) and Pugh and Cameron (1976) show the greatest similarities. However, there are several differences as well. Particularly the choriocarcinoma group (group V according to Dixon and Moore) and the MTT cannot be properly compared because the British classification regards all tumours containing choriocarcinoma as MTT, whereas in the classification of Dixon and Moore (1953) they are divided over several groups.
These differences in histological classification may preclude or impede comparison of therapeutic results. Moreover, it is precisely those therapists who use the British classification who advocate radiotherapy for non-seminomatous tumours of the testis. In addition, as will be discussed in section V.5, the difference in therapeutic approach also determines a difference in clinical staging.
In view of these three different concepts concerning histology, staging and therapy, great prudence is imperative in comparing patients treated surgically with those given radiotherapy. As regards the histological classification, all primary testicular tumours as well as the metastases would have to be classified according to all the different systems if at least these factors are to be eliminated.

V.3 Theories on the histogenesis of malignant testicular tumours

Apart from different views on histological classification, the histogenesis of malignant testicular tumours is likewise a controversial subject, and again we find British and American views clashing. The principal point of discussion is whether teratomas or non-seminomatous tumours originate from germ cells or from cells changed in the course of embryonic development. The germ cell theory was originally advanced by Ewing (1911) and later taken over by Friedman and Moore (1946) and by other American pathologists. This theory is based on the postulate that all malignant testicular

tumours originate from the germ cell, which can differentiate into a seminoma or an embryonal carcinoma. Embryonal carcinomas consist of totipotential cells, which as in the foetus can develop in the direction of embryonic tissues (ectoderm, mesoderm, endoderm) or in the direction of extra-embryonic tissues (trophoblast = choriocarcinoma; yolk-sac = yolk-sac tumour) (Pierce and Abell 1970).
Skakkebæk and Berthelsen (1981) propose a revision of this germ cell theory. These authors suggest, that both the seminomas as the non-seminomatous tumours originate from the cell showing the carcinoma-in-situ pattern. An exception is possible the spermatocytic seminoma, which may originate from spermatocytes.
The theory postulating changes in cells during embryonic development was first advanced by Willis (1960) and later defended by Collins and Pugh (1964). All in all, the British school holds that the origin of malignant testicular tumours is rather obscure. Gradually, however, and mostly in view of the results of animal experiments, British investigators seem to be inclined more in favour of the germ cell theory. But as long as the animal experiments cannot be reduplicated with human tumour cells, they continue to discern an element of uncertainty in this theory (Pugh and Cameron 1976).

V.4 Incidence of histological types

Germ cell tumours represent about 96% of all malignant testicular neoplasms, the remaining 4% comprising non-germ cell tumours such as malignant lymphomas and tumours arising from interstitial cells.
Seminomas are the most common of the germ cell tumours, although different authors report different incidences. The same applies to the non-seminomatous germ cell tumours of the testis. Table V.2 presents the distributions of histological types reported by a number of authors, who used the classification of Dixon and Moore (1953). The figures in the various series are very similar. However, since all these series are based on data from the American Armed Forces there has been selection of patients. The result is a relatively low incidence of seminomas, which develop at a later age than non-seminomatous tumours. In a survey of the literature on the relative incidence of seminomas published by Blandy et al. (1970), this is shown to range from 23% to 87%; and it is precisely in the "military series" that a lower seminoma incidence is seen.

	Dixon and Moore (1953)	Patton et al. (1960)	Kurohara et al. (1967)
Pure seminoma (I)	40.6	36.1	33.6
Embryonal carcinoma with or without seminoma (II)	29.9	31.1	32.1
Teratoma, with or without seminoma (III)	9.2	2.5	2.5
Teratoma with embryonal carcinoma and/or chorio-carcinoma and with or without seminoma (IV)	19.0	26.1	27.0
Choriocarcinoma with or without embryonal carcinoma and/or seminoma (V)	1.1	1.8	1.5
Others	—	2.4	3.0
Total	990	570	196

Table V.2: Distribution of histological types of germ cell tumours of the testis. (classification according to Dixon and Moore (1953)).

Choriocarcinomas are the least common of the non-seminomatous germ cell tumours. In the American series, only tumours which consist solely or largely of trophoblast cells are so defined. In the British series, however, the term Malignant Teratoma Trophoblastic (MTT) covers all non-seminomatous tumours which contain trophoblast cells. This is why the incidence of MTT in the British series exceeds that of choriocarcinomas in the American series. In the series of Dixon and Moore (1953) the choriocarcinoma incidence was 1.1%, whereas that in the series of the British Testicular Tumour Panel was 3.8% (Pugh and Cameron 1976). The prognosis of MTT is therefore generally better than that of choriocarcinoma in the classification of Dixon and Moore (1953).

A separate germ cell tumour which occurs especially in children but is also seen in adults (in which case it is usually combined with other histological types) is the infantile embryonal carcinoma (synonyms: yolk-sac tumour, endodermal sinus tumour, orchioblastoma, adenocarcinoma of the infantile testis, adenocarcinoma with clear cells). This tumour is not separately specified in the classification of Dixon and Moore (1953), but it is in the

more recent classifications (table V.1). Talerman (1975) found infantile embryonal carcinoma elements in 38% of a group of 68 non-seminomatous tumours. These elements were predominant in 11%. In this series, the prognosis was found to be less favourable in the adults whose tumour contained this component.

V.5 Staging

While there may be evidence of some agreement on the histological classification of malignant testicular tumours, clinical staging is still an entirely controversial subject. The primary purpose of staging is to distinguish groups or subgroups of patients with a more or less comparable prognosis; the secondary purpose is to ensure uniformity of therapeutic approach per group.

The oldest system of clinical staging of malignant testicular tumours is that proposed by Boden and Gibb in 1951. These authors divided the patients into three groups: stage I (tumour limited to the testis); stage II (tumour metastases only caudal to the diaphragm); stage III (tumour spread cranial to the diaphragm). This system initially seemed satisfactory, but with increasing therapeutic experience and improved results it was found to be inadequate. Yet in principle all subsequent staging systems are in fact based on that of Boden and Gibb (1951) and recognize the basic stages I, II and III. It is in the substages that many variations have been suggested (Table V.3).

The TNM classification of malignant testicular tumours is based in principle on clinical, not on histological data, although the latter may be used. The designation used in this respect is "postoperative histopathological classification" (pTNM). As chapter IV has shown, this differs from the TNM classification. We also find that the TNM system refers to the supraclavicular lymph node metastases as juxta-regional lymph node metastases, and stages them as N_4. Others consider patients with supraclavicular metastases to be in stage III, because these metastases are localized cranial to the diaphragm.

Of course these differences can give rise to problems in comparing therapeutic results. An advantage of the TNM system, and of the staging system of the American Joint Committee (1977) which can be equated with it, is that the extent of primary tumour is indicated. It remains to be seen, however, whether the extent of the primary tumour influences the prognosis (Fraley et al. 1980).

Staging system as mentioned by Skinner and Scardino (1980) (UCLA School of Medicine).

Stage I	Tumour confined to the scrotum, negative nodes and no other evidence of disease.
Stage IIA	Metastases fewer than 6 retroperitoneal nodes, with no node > 2 cm in diameter.
Stage IIB	Metastases to 6 or more retroperitoneal lymph nodes or any metastasis > 2 cm in diameter, or extracapsular spread.
Stage IIC	Bulky abdominal disease detected grossly on abdominal examination before operation, usually associated with significant ureteral deviation and/or obstruction.
Stage III	Metastases above the diaphragm or to the viscera (liver).

Staging system for testicular tumours at the University of Minnesota (Fraley et al. 1979a).

Stage I	Tumour confined to the testis.[1])
Stage II	Metastases in the retroperitoneum only unless inguinal lymphatics have been contaminated by transscrotal procedure or previous inguinal operation: then inguinal nodes may contain tumour.
IIS	Serum marker levels elevated before lymphadenectomy but return to normal afterwards: no tumour found in the nodes.[2])
IIA	Microscopic tumour involving 6 or fewer well-encapsulated nodes.
IIB	Small amount of visible tumour *or* microscopic tumour involving more than 6 nodes *or* microscopic extension of the tumour into the retroperitoneal fat.
IIC	Bulky tumour involving large amount of retroperitoneal fat with all visible disease resected.
IID	Same as IIC but resection of all visible disease not possible.
Stage III	Metastases outside retroperitoneal nodes.
IIIA	Apparently single metastasis.
IIIB	Multiple metastases.

[1]) The pathology report should include any information on invasion of local structures. If the inguinal lymphatics have been contaminated, the pathologic findings at hemiscrotectomy and groin dissection are considered when assigning stage.

[2]) Elevation not accounted for by marker produced by the primary tumour.

U.I.C.C. Staging System for the Testicular Tumours (1979).

T — Primary Tumour

In the absence of orchiectomy the symbol T_X must be used.

T_X The minimum requirements to assess fully the extent of the primary tumour cannot be met.

T_0 No evidence of primary tumour.

T_1 Tumour limited to the body of the testicle.

T_2 Tumour extending beyond the tunica albuginea.

T_3 Tumour involving the rete testis or epididymis.

T_4 Tumour invading the spermatic cord or scrotal wall.
- T_{4a} Invasion of the spermatic cord.
- T_4b Invasion of the scrotal wall.

N — Regional and Juxta-regional Lymph Nodes.

The regional lymph nodes are the para-aortic and para-caval nodes. Following scrotal surgery the homolateral inguinal lymph nodes are included with the regional lymph nodes. The juxta-regional lymph nodes are the intrapelvic nodes and the mediastinal and supraclavicular nodes.

N_X The minimum requirements to assess the regional lymph nodes cannot be met.

N_0 No evidence of involvement of regional lymph nodes.

N_1 Involvement of a single homolateral regional lymph node which, if inguinal, is mobile.

N_2 Involvement of contralateral or bilateral *or* multiple regional lymph nodes which, if inguinal, are mobile.

N_3 A palpable abdominal mass is present *or* there are fixed inguinal lymph nodes.

N_4 Involvement of juxta-regional nodes.

M — Distant Metastases.

As the primary tumour advances or if clinical suspicion warrants skeletal or isotope studies should be done.

M_X The minimum requirements to assess the presence of distant metastases cannot be met.

M_0 No evidence of distant metastases.

M_1 Distant metastases present.
- M_{1a} Evidence of occult metastases based on biochemical *and/or* other tests.
- M_1b Single metastasis in a single organ site.
- M_{1c} Multiple metastases in a single organ site.
- M_{1d} Metastases in multiple organ site.

The location of the metastases should be specified. The lymph node beyond the regional and juxta-regional nodes, and bone are regarded each as single organ sites.

Table V.3: Review of the most widely used staging systems.

Sandeman and Matthews (1979) found no marked differences in prognosis between the various subgroups with differences in primary tumour extent. A difference in survival was demonstrable, however, when the scrotum wall was involved in the process or when blood and/or lymphatic vessels were invaded. The authors propose to modify the TNM system on this point, and to stage the group with invasion of blood and/or lymphatic vessels as T_2, versus T_1 for all other types of local tumour extent.
On the other hand, Batata et al. (1980) found no correlation whatever between T category and metastases and survival.
The local extent of primary tumour was also taken into account in the Groningen study, and chapter XII will discuss this point.
The literature shows that there is no uniform subdivision of stage II, and that in some instances the clinical and pathological classifications are mixed. In our study we have opted in favour of the staging system of Skinner and Scardino (1980), which virtually equates with that of Fraley et al. (1979) (table V.3). This system is the one most widely used in the USA, and is based on pathological findings. We have always distinguished between minimal disease, bulky disease and an intermediate stage.
The number of nodes containing metastases is of importance, as is the size of the nodes and microscopic evidence of tumour tissue outside the lymph node capsule. Whether the lymph node metastases are restricted to the ipsilateral side is irrelevant in this staging system; nor is it important whether there are para-iliac metastases. But in the TNM classification, which is based on clinical data, these points are emphasized.
Sandeman and Matthews (1979) question whether this has any prognostic significance (with justification, in our opinion). They concluded from their findings that the principal criterion in clinical studies is whether metastases are present or absent (N_0 and N_1, respectively). These authors classify a palpable tumour as N_2, and the presence of supraclavicular metastases as N_3.
Peckham et al. (1979) used lymphography, CT-scan and echography in an attempt to refine the criterion "size of retroperitoneal metastases". In this respect they distinguish three subgroups: stage IIA (lymph nodes with a maximum diameter of 2 cm), stage IIB (lymph node diameter 2-5 cm) and stage IIC (lymph node diameter in excess of 5 cm). In view of the therapeutic results, this substaging would seem to have a rational basis in spite of the limitations of these techniques (see section VI.7).
It is still not quite clear how metastases in inguinal lymph nodes should be classified. The TNM system includes them among the locoregional lesions.

Most other authors do not include inguinal metastases in staging. They are in fact a form of regional spread. Inguinal metastasis of a malignant testicular tumour results from changes in lymph drainage (e.g. due to previous operations in the inguinal region) or from contamination of the scrotum wall in a scrotal tumour operation.
We maintain that patients of this group should be separately mentioned because the finding of inguinal metastases has therapeutic implications. Whether it is of prognostic significance as well, is unknown.

While the staging of regional metastases is still controversial, there is fair agreement about that of distant metastases. Solitary and multiple metastases are generally distinguished. In terms of prognosis it would seem to be of little importance whether the tumour has metastasized only to the lungs or to other organs as well. It is nevertheless to be noted that Sandeman and Matthews (1979) found a distinctly less favourable prognosis in those patients of their series who had metastases in several organs. Some authors also differentiate on the basis of the size of distant metastases (Peckham et al. 1979). With the increasing use of polychemotherapy in advanced stages of the disease, more accurate staging on the basis of distant metastases will probably be required.
The possibility of demonstrating minimal amounts of tumour tissue with the aid of tumour markers (HCG and AFP) has added another element to the staging systems. They have played a role in particular in the staging system used at the University of Minnesota (Fraley et al. 1979). Fraley et al. (1979) distinguish a stage IIS, in which tumour markers were increased before retroperitoneal lymph node dissection but returned to normal afterwards, although no tumour tissue was demonstrable in the resected specimen.
Another wellknown dilemma is the patient with persistently increased tumour markers after retroperitoneal lymph node dissection, in the absence of demonstrable metastases. Obviously such a finding has implications for further therapy.
In conclusion it can be stated that the staging of malignant testicular tumours is fairly chaotic. This is partly due to differences in views on therapy which cause the continued use of two different types of staging: one based on clinical and one based on histological data. In Groningen we have opted in favour of a staging system based on pathological findings (Skinner and Scardino 1980) which, with minor modifications, is used by many advocates

of primary surgical therapy. One advantage of this system is that, in actual practice, consequences for the treatment of patients in the various substages II are already being drawn (see chapter VI).

CHAPTER VI

METHODS OF TREATMENT FOR PATIENTS WITH A NON-SEMINOMATOUS TUMOUR OF THE TESTIS

VI.1 Introduction

The results of treatment in patients with malignant testicular tumours have improved in the course of the 20th century owing to developments in surgical techniques, radiotherapy and chemotherapy. The treatment of choice for non-seminomatous tumours of the testis, however, remains to be established. There are still marked differences in views on therapeutic methods, and consequently it is virtually impossible to compare the results reported. The controversy focuses in particular on the treatment of retroperitoneal lymph node metastases.

This chapter presents a review of possible therapies and, because differences in views are intimately related to historical developments, the history of the treatment of patients with a malignant testicular tumour is briefly outlined.

VI.2 Historical developments

The treatment of patients with a malignant testicular tumour consisted solely of orchiectomy until the end of the previous century. The 4-year survival was 15-20% (Chevassu 1906, Coley 1915).

At about the turn of the century, the concept of removing not only the tumour but also the lymphatics and lymph nodes of the drainage area was not new. The procedure had already been performed in cases of breast carcinoma (Halsted 1894). When more information on the lymph drainage system of the testes became available - mostly in studies published by Most

(1899) - the notition of performing a similar procedure in the treatment of testicular tumours was born.

It had long been known that metastases of malignant testicular tumours can be found in the abdomen. The first step in the direction of node dissection was an attempt to remove a retroperitoneal mass, first reported in the literature by Kocher (1887). On 28th December 1883 he removed a tumour with the size of a man's head from the retroperitoneal region. Five months later, however, recurrence was observed. In 1905, Foulerton reported on a similar but entirely successful operation performed in 1895.

In the early years of the 20th century, French and English publications reported on more systematically performed dissections. Via a lumbar incision - but remaining retroperitoneal - the ipsilateral lumbar lymph nodes were dissected (Chevassu 1906, 1910; Bland-Sutton 1909; Delbet 1910; Howard 1910; Marion 1910). A transabdominal lymph node dissection had already been performed by the American Roberts (1902), but his patient died of peritonitis.

In Europe, the radical operation was advocated especially by Chevassu (1906, 1910). He regarded the earlier operations, as performed by Kocher, as too dangerous and ineffective, and therefore rejected them. He maintained that dissection of the tumour from the aorta and the inferior vena cava was beyond the limits of surgical feasibility, and contended that metastases palpable through the abdominal wall, could not be removed. Chevassu also rejected the method of Villar (1902) who, wishing to do more than orchiectomy, extended the incision so far in cranial direction that the para-iliac nodes could be resected as well. Precisely with this procedure, however, it was impossible to remove the primary lymph node sites.

The promotor of lymph node dissection in the USA was Hinman (1914, 1919). In 1923 he published a review of 79 patients treated by a so-called radical operation since the turn of the century, and compared these results with those of orchiectomy as only treatment. His conclusion was that results had improved 100%: while orchiectomy led to a cure in only 15% of patients, a radical operation did in 30%.

Yet there was also opposition to the extensive operation. Coley (1915) pointed out an operative mortality of 10-15%. Was such a risky and major operation justifiable when no positive lymph nodes were found in about 50% of cases? Coley recommended treatment by administration of toxins. He injected patients with a malignant testicular tumour with a mixture of Bacillus prodigiosus toxin and a filtrate of haemolytic streptococci (Coley's

fluid). The results were encouraging. The effect of this therapy was probably based on hyperthermia caused by the toxins (Dickson 1979).

Radiotherapy was introduced in the treatment of malignant testicular tumours in the second decade of this century. The literature on initial developments, however, is scanty. Beclère (1916) was probably the first (in 1905) to use radium in a successful attempt to destroy a retroperitoneal lymph node metastasis. In 1920 the Dutchman Orbaan described a series of patients with metastases of testicular or ovarian carcinoma, treated by radiotherapy in the Antoni van Leeuwenhoek Hospital (Amsterdam). Although this treatment was palliative, favourable effects were observed. Hinman (1919) had previously recommended leaving an in-dwelling catheter with radium in the area of operation after a lymph node dissection. The catheter was to be removed after a few hours.

A more systematic approach was described by Barringer and Dean (1921), who irradiated the affected testis with radium before orchiectomy. In this way they gained an impression of the sensitivity of the primary tumour to radiotherapy. After orchiectomy (and retroperitoneal lymph node dissection, if possible) local radium irradiation followed.

Until that time, dissections had been performed regardless of whether the testicular tumour was a seminoma or non-seminomatous tumour. It seems likely that the good results of radiotherapy in seminoma cases caused retroperitoneal lymph node dissection to recede into the background in the Thirties (Cooper et al. 1950). Even Hinman (1933, 1935), the staunch advocate of the operation in the USA, moderated his views. He advocated dissection only for radio-resistant tumours, and in cases with an abnormal Ascheim-Zondek reaction.

The first report on operative treatment of malignant testicular tumours to reappear in the literature was that published by Lewis in 1948. His conclusion was that seminomas required orchiectomy and radiotherapy, while the other tumours should be treated by orchiectomy, lymph node dissection and radiotherapy. Although Hinman (1933, 1935) had reached a similar conclusion 15 years earlier, it was only now that the difference in treatment between patients with a seminoma and those with a non-seminomatous tumour came to the fore. The discussion in subsequent years was concerned less with the indication for lymph node dissection than with the technique of the operation.

Until the early Fifties, the operation continued to be performed in the manner described by Chevassu (1906, 1910) and later by Hinman (1914). In

1950, Cooper et al. introduced the thoraco-abdominal approach via the bed of the 11th rib, which gave better access to the nodes around the renal vascular pedicle. Variations of this procedure were introduced by others (Vallet 1952; Lewis et al. 1952). Until that time, dissection had been confined to the ipsilateral lymph nodes. In 1953, however, Leadbetter proposed that, in cases with histologically positive lymph nodes, a contralateral dissection should be performed in a second stage even if no positive nodes were palpable. However, the unilateral approach was not satisfactory for a one-stage procedure. Mallis and Patton (1959) and Stehlin et al. (1959) described the transabdominal approach, thus imitating Roberts who had performed a lymph node dissection by this route more than half a century earlier (1902). The thoraco-lumbar approach, however, has not been abandoned, and discussions on the approach of choice still continue.

VI.3 Surgical treatment

The first step in the treatment of a testicular tumour suspected of malignancy is of course orchiectomy with high ligation of the vasa spermatica and ductus deferens. While it is unanimously agreed that treatment of a seminoma should consist of orchiectomy followed by radiotherapy, views on the treatment of the retroperitoneal lymph nodes in patients with nonseminomatous tumours differ widely. The sensitivity of seminomas to radiotherapy does not justify retroperitoneal lymph node dissection, even though it has long been customary to perform it (see section VI.2). As recently as 1968, Maier et al. concluded that in seminoma patients no significant improvement can be achieved by adding retroperitoneal lymph node dissection to radiotherapy. Non-seminomatous tumours, however, are far less sensitive to irradiation in doses not injurious to normal tissues. Yet radiotherapy of the para-aortic and para-iliac lymph nodes after orchiectomy is still routine procedure at many centres. It is only when radiological examination demonstrates a residual tumour that surgery is resorted to at some of these centres (Smithers 1976). It can be stated in general terms that advocates of radiotherapy are to be found in Great Britain, while advocates of retroperitoneal lymph node dissection are Americans. Continental European views as a rule differ from centre to centre.

VI.3.1 *The purpose of laparotomy/lymph node dissection*

The principal indication for laparotomy/retroperitoneal lymph node dissection is to achieve optimal accuracy in staging the tumour process

(Johnson 1977; Schraffordt Koops et al. 1978). The discussion of pedal lymphography as a clinical aid in the diagnosis of retroperitoneal lymph node metastases has already shown that the reliability of this method is limited. It can be enhanced by using other techniques such as CT-scan, echography, aortography, cavography and lymphography via the spermatic cord, if necessary, but no complete correlation between the results of these methods and histological findings has so far been observed. Consequently, if one relies solely on the data of clinical staging, not performing laparotomy/ retroperitoneal lymph node dissection, then some patients are bound to receive treatment which is not commensurate with the stage of disease they have reached. This applies in particular to patients in whom histological examination failed to disclose lymph node metastases.

Precisely the accurate dissection of the lymph nodes as staging procedure can prevent unjustified radiotherapeutic treatment. And in this way a whole range of possible complications of radiotherapy (intestinal, renal and bone marrow lesions) can be avoided. Particularly the last-mentioned complication can restrict such chemotherapy as may be required (Johnson 1977; Donohue 1977b; Stoter et al. 1979; Oliver et al. 1980). Although retroperitoneal lymph node dissection may give rise to ejaculation disorders, we hold that this complication can now be adequately treated (Nijman et al. 1981).

A second reason for retroperitoneal lymph node dissection is the possibility of removing metastases. In this respect we proceed according to the principle that any micrometastases which may remain in situ are more easily treated by adjuvant chemotherapy than larger metastases which are not removed. We believe that regional recurrence can be prevented in this way (Schraffordt Koops et al. 1978).

A third reason for surgical evaluation of the retroperitoneal nodes is assessment of the effect of chemotherapy. As our series shows, node dissection may in some cases be impossible at the time of the first laparotomy. After chemotherapy, however, the metastases are often so far in regression that removal is possible. Further chemotherapeutic management is then indicated (Johnson 1977; Schraffordt Koops et al. 1978).

In more advanced stages of the disease, too, dissection of retroperitoneal lymph nodes after regression of a palpable abdominal tumour, pulmonary metastases and/or supraclavicular lymph node metastases in response to chemotherapy can give an impression of the effect of this treatment. In many of these cases it is found that only mature teratoma is still present

(Einhorn and Donohue 1977; Johnson 1977; Stoter et al. 1979; Hendry et al. 1980).

As already indicated in the introduction, the argument that laparotomy/ retroperitoneal lymph node dissection permits staging is the principal point of contention between advocates and opponents of operative therapy. The complication of ejaculation disorders is the principal argument used against surgical therapy. As long as there is no uniformity in histological classification and as long as the staging methods used differ from centre to centre, however, it will be impossible to establish with certainty which method of treatment is to be preferred.

We consider the arguments in favour of retroperitoneal lymph node dissection to be sufficiently convincing to accept the postulate that a patient with a non-seminomatous tumour of the testis should in principle receive surgical treatment (or staging).

The treatment of patients with a non-seminomatous tumour of the testis is discussed in detail in the following sections. The therapeutic approach in which retroperitoneal lymph node dissection is of central importance is first reviewed. Next, the purely radiotherapeutic approach to this group of patients receives attention.

VI.4 Primary surgical treatment of patients with a non-seminomatous tumour of the testis in stage I

As already explained in chapter V, we define stage I as the stage in which the tumour is evidently limited to the testis. This can only be stated with certainty when retroperitoneal lymph node dissection with histologically negative nodes and adequate radiological examination of the lungs has demonstrated it.

The literature shows that advocates of retroperitoneal lymph node dissection still hold different views on the proper management of this initial stage of the disease. It is consequently difficult to compare different types of surgical treatment. To begin with, there are controversial views on the extent of the intervention. Should bilateral or unilateral retroperitoneal lymph node dissection be performed? Should the dissection be extended to levels cranial to the renal vascular pedicle?

The second point of discussion is whether dissection should be followed by radiotherapy. An alternative possibility is to give radiotherapy both before and after the operation (so-called "sandwich" technique). Finally: should chemotherapy follow surgical treatment?

In actual practice, differences in views on the extent of discussion have proved not to influence therapeutic results. Johnson et al. (1976) found a 5-year survival of 87.5% after bilateral, and 92.6% after unilateral retroperitoneal lymph node dissection in stage I. The difference proved not to be significant. Nor were these authors able to demonstrate a significant difference in 5-year survival between patients with left-sided and those with right-sided tumours.

Previously, Walsh et al. (1971) had likewise concluded that there is no difference in survival between unilateral and bilateral lymph node dissection. Because left-sided testicular tumours do not metastasize to the contralateral side without producing homolateral metastases (Ray et al. 1974), Johnson et al. (1976) confined themselves to unilateral dissection in all patients with a left-sided tumour. Bilateral dissection was performed when the tumour was localized in the right testis.

The principal reason for unilateral lymph node dissection was believed to be the chance of maintaining normal antegrade ejaculation (because the contralateral sympathetic trunk remains intact). However, Johnson (1977) found that normal ejaculation was discontinued also after unilateral dissection. Kedia et al. (1975) likewise reported ejaculation disorders in 94% of patients after unilateral lymph node dissection. It is therefore evident that unilateral retroperitoneal lymph node dissection does not guarantee continued antegrade ejaculation, and that this is no reason to opt in favour of a unilateral procedure.

Whether dissection involving the nodes between diaphragm and renal vascular pedicle is to be preferred in stage I, has not been established with certainty. Theoretically, so extensive a dissection is not necessary because the primary lymph node sites are localized caudal to the renal vessels on either side of aorta and inferior vena cava. In exceptional cases, primary lymph node sites can be found also cranial to the renal vessels, as Donohue et al. (1977) reported in two patients out of a group of 60. Staubitz et al. (1973, 1979) refrain from retroperitoneal lymph node dissection when metastases are found cranial to the renal vessels. In our Groningen department, too, the renal vessels are accepted as demarcation of the upper limit of dissection, and patients with suprahilar metastases are not treated primarily by dissection.

The literature so far provides no evidence that therapeutic results can be improved by extending node dissection to levels cranial to the renal vascular pedicle (Fraley et al. 1979b).

As already mentioned, views on postoperative management in stage I also differ. In our department we confine ourselves to lymph node dissection and subsequent follow-up. The results thus obtained will be discussed in chapter IX. At other centres, too, patients with non-seminomatous tumours are treated in this way. Table VI.1 presents a survey of results reported by the various authors. These data make no difference between unilateral, extended unilateral, and bilateral lymph node dissection.

	3-year survival	5-year survival
Castro (1969)	27/32 (84%)	—
Whitmore (1970)	—	43/49 (88 %)
Walsh et al. (1971)	24/25 (96%)	—
Staubitz et al. (1974)	42/45 (93%)	31/36 (86 %)
Johnson et al. (1976)	—	72/ (90.8%)
Hussey et al. (1977)	71/85 (83%)	—
Donohue et al. (1979)	30/30 (100%)	—

Table VI.1: Non-seminomatous tumours of the testis stage I. 3-year and 5-year survival after retroperitoneal lymph node dissection.

This table shows that the 3-year survival ranges from 83% to 100%, and the 5-year survival from 86% to 91%.

A patient with a non-seminomatous tumour of the testis who survives three years and in whom no tumour is demonstrable at that time, is generally regarded as cured. In a study of 834 patients with a malignant testicular neoplasm, Nefzger and Mostofi (1972) found the highest mortality in the first few years after treatment. Patients who survived two years without demonstrable tumour growth had the same life expectancy as normal males of comparable age in 85% of cases. The corresponding figures for 5-year and 10-year survivors were 93% and 96%. These findings show that 3-year and 5-year survivals do not necessarily equate to a cure, although the chance of a definite cure increases with increasing time. The study of Nefzger and Mostofi, however, is dated 1972, and therapeutic methods (and consequently results) have since been markedly improved. For patients with a non-seminomatous tumour of the testis 3-year survival is a widely applied criterion to evaluate the results of treatment. In our study, too, 3-year survival without demonstrable tumour growth is used as such a criterion.

Castro (1969), Staubitz et al. (1973, 1979) and Johnson et al. (1976) found no retroperitoneal tumour recurrence in any of their stage I patients after

death due to metastases. All had metastases in other organs, but in this context it should be pointed out that pulmonary metastases are of course more readily detectable than retroperitoneal lymph node metastases.

Table VI.2 outlines the results of retroperitoneal lymph node dissection followed by radiotherapy, generally at a dosage of 2000-3000 rad (20-30 Gy) in 4-5 weeks. The figures indicate that survival cannot be enhanced by adding irradiation to lymph node dissection.

	3-year survival
Castro (1969)	17/19 (89%)
Walsh et al. (1971)	4/5 (80%)
Bradfield et al. (1973)	17/27 (63%)
Hussey et al. (1977)	3/3 (100%)

Table VI.2: Non-seminomatous tumours of the testis stage I. 3-year survival after retroperitoneal lymph node dissection followed by radiotherapy.

Another form of therapy involves the so-called "sandwich" technique: radiotherapy both before and after the operation; the preoperative dosage is 2000-3000 rad (20-30 Gy) in 4 weeks, while that after operation is 1500-2500 rad (15-25 Gy) in 3 weeks (mean tumour dose 4500 rad (45 Gy)). A survey of the results thus obtained is presented in table VI.3.

	3-year survival	5-year survival
Earle et al. (1973)	12/12 (100%)	—
Nicholson et al. (1974)	23/27 (85%)	—
Quivey et al. (1977)	—	7/7 (100%)
Hussey et al. (1977)	17/20 (85%)	—
Maier and Mittemeyer (1977)	29/30 (97%)	—
Lynch et al. (1978)	7/7 (100%)	—

Table VI.3: Non-seminomatous tumours of the testis stage I. 3-year and 5-year survival after retroperitoneal lymph node dissection and "sandwich" technique.

The results with this "sandwich" technique are comparable with those obtained by retroperitoneal lymph node dissection alone. It should be noted that the series discussed in the literature are generally small. The principal reasons for preoperative radiotherapy were formulated by Dijkhuizen et al.

(1968). There should be a reduction in the size and the vitality of the metastatic process, therefore reducing the risk of transplantation metastasis. Moreover, preoperative radiotherapy is held to be more effective because at that time the tumour cells are still well-oxygenated. Hussey et al. (1977) found retroperitoneal node metastases in only 27.7% of patients given preoperative radiotherapy, versus 88.9% of the patients treated by dissection without preoperative radiotherapy. It should be borne in mind that this was not a randomized study, and that only clinical staging was done.

An attempt to determine the contribution of radiotherapy to the results of retroperitoneal lymph node dissection in stage I reveals that dissection per se is sufficient in this stage. In fact the additional radiotherapy seems even harmful and therefore contraindicated. Although the dosage is not excessive, there is always a risk of intestinal lesions, particularly because a laparotomy has preceded the irradiation. Gennari et al. (1979) found abdominal complications in as many as 10% of patients treated by operation and irradiation with more than 3750 rad (37.5 Gy). At the dosages used, renal lesions are likewise always possible (Maier and Lee 1977). The long-term effect of radiotherapy in this group of young adults is still unknown. It is virtually certain, however, that in the case of recurrence the risk is increased when chemotherapy is required (Donohue et al. 1977; Stoter et al. 1979). The radiotherapy has damaged the bone marrow, and consequently effective doses of cytostatics are less well tolerated. The more important reason, however, is that it is illogical to irradiate the retroperitoneum when no tumour tissue has been found in it. Moreover, the additional radiotherapy increases the total duration of treatment and thus increases the expenses involved.

It is uncertain whether adjuvant chemotherapy has any significance in the treatment of non-seminomatous tumours of the testis in stage I. In view of the fact that metastases of a testicular tumour are nearly always found in the lungs after primary surgical treatment, Skinner (1976a) advises routine use of chemotherapy in stage I. The first course is started during the operation, and therapy totals two courses of actinomycin-D (3-5 mg during 5 days). When the primary tumour contains choriocarcinoma tissue, actinomycin-D is supplemented with bleomycin and vinblastine during two years. This method enhanced survival from 82% to 93%, but it should be noted that this series also included stage II patients with fewer than six positive lymph nodes and without invasion of lymph node capsules. In a subsequent publica-

tion on the same therapy (Skinner and Scardino 1980) the 3-year survival in stage I was reported as 100% (series of 56 patients); two patients who developed metastases were salvaged by chemotherapy.

A new point of discussion has arisen since the introduction of the radio-immuno-assay has made it possible to demonstrate low concentrations of tumour markers as parameters of the presence of tumour tissue. If one or both tumour markers show an increased concentration before orchiectomy but normalization is seen after it, should retroperitoneal lymph node dissection still be performed for staging purposes? Randomized prospective studies will have to show whether clinical diagnostic methods suffice or whether laparotomy with possible lymph node biopsies is the staging procedure of choice.

The results of surgical treatment of patients with a non-seminomatous tumour alone or combined with radiotherapy, are not the same for the various histological tumour types. In the above-mentioned series the pure choriocarcinoma group was generally omitted because it is a separate group. This tumour is known to produce mostly (early) haematogenous metastases. However, this series includes non-seminomatous tumours with choriocarcinoma components (group IV in the classification of Dixon and Moore 1953). Most publications lump the various histological types together, and only a few authors report therapeutic results for the various histological types separately. Table VI.4 presents a survey of therapeutic results reported in stage I in accordance with the classification of Dixon and Moore (1953). Choriocarcinoma is listed for the sake of completeness.

This table seems to indicate that therapeutic results in embryonal carcinoma are less favourable than those in teratomas or tumours which contain teratoma components. However, it is especially in series of less recent date that the difference in survival occurs. The series reported by Skinner (1976, 1977), Lynch et al. (1978) and Donohue et al. (1979) show no difference in survival between the embryonal carcinoma group and the teratoma/teratocarcinoma group. The results reported by these investigators have not been included in the table because they used the Friedman and Moore classification (1946).

	Bradfield et al. (1973)		Staubitz et al. (1974)		Johnson et al. (1976)
	3-year survival	5-year survival	3-year survival	5-year survival	5-year survival
Embryonal carcinoma ± seminoma	10/21 (48%)	7/19 (37%)	26/28 (93%)	20/23 (87%)	13/18 (72%)
teratoma ± seminoma	5/5 (100%)	5/5 (100%)	11/11 (100%)	7/8 (87%)	18/18 (100%)
teratoma and embryonal carcinoma and/or choriocarcinoma ± seminoma	30/38 (79%)	23/30 (77%)	4/4 (100%)	3/3 (100%)	33/36 (92%)
choriocarcinoma ± seminoma	1/2 (50%)	1/3 (33%)	1/2 (50%)	1/2 (50%)	

Table VI.4: Non-seminatous tumours of the testis stage I. 3-year and 5-year survival of the histological types according to the classification of Dixon and Moore (1953).

VI.5 Primary radiotherapy in the treatment of patients in clinical stage I

It should be borne in mind that the clinical stage I of patients treated by radiotherapy differs from the stage I from which we proceeded in the patients treated by primary surgical therapy. There is no exact information on involvement of the retroperitoneum in patients treated by primary irradiation. As already stated in subsection IV.3.1, the rate of false negative lymphographic findings ranges from 62% to 86%. This means that the disease in about 20-25% of patients in clinical stage I is already so far advanced that they should be classified in pathological stage II. Of course the majority of patients in this group have only minimal lesions, but larger metastases can also give false negative findings.

In this respect, it is impossible to compare the results of retroperitoneal lymph node dissection with those of radiotherapy in the various stages. Other differences which impede comparison have been discussed in chapter V. Nevertheless, the two approaches to the retroperitoneum are constantly being compared in the literature. As long as no randomized study has been designed to demonstrate the superiority of one of these approaches for each of the separate histological types, however, the two methods of treatment cannot be properly compared.

In order to give an impression of the results of primary radiotherapy for patients with a non-seminomatous tumour of the testis a survey will be

presented. Irradiation is usually given at a dosage of 4000 rad (40 Gy) in 4-5 week on the lumbar and the ipsilateral iliac region. Mediastinum and supraclavicular nodes are not routinely included in the irradiation. The 3-year survival in clinical stage I proves to range from 64% to 90%, as shown in the survey in table VI.5.

	3-year survival	5-year survival
Castro (1969)	8/10 (80%)	—
Tyrrell and Peckham (1976)	74/78 (84%)	—
v.d. Werf-Messing (1976)	26/29 (90%)	idem
Blandy et al. (1976)	49/77 (64%)	43/77 (56%)
Maier and Mittemeyer (1977)	25/29 (86%)	—
Tierie et al. (1979)	28/34 (82%)	—

Table VI.5: Non-seminomatous tumours of the testis clinical stage I. 3-year and 5-year survival after orchiectomy and radiotherapy.

Only the study published by Maier and Mittemeyer (1977) was prospective and randomized. Pure choriocarcinomas were excluded from this study. In the other arm of the study was a series of patients treated by the "sandwich" technique, with a 3-year survival of 97%. In this series, however, no distinction was made between the various histological types.

As already mentioned, the older series in particular show that after primary surgery embryonal carcinomas have a less favourable prognosis than tumours containing teratoma components. A similar difference is found in the groups given primary radiotherapy. Blandy et al. (1976) reported a 3-year survival of 89% in stage I patients with MTI (teratocarcinomas) versus 25% in those with MTU (embryonal carcinomas). In the series published by Van der Werf-Messing (1980), too, the prognosis in stage I patients with MTIA was excellent (14/14: 100%) while that in the MTA group was far less favourable (75%).

A possible cause of the difference in therapeutic result between the various histological types is that MTU (formerly MTA) (embryonal carcinomas) show earlier haematogenous metastasis (Van der Werf-Messing 1976; Blandy et al. 1976). It is remarkable that precisely tumours with teratoma components show a better response to radiotherapy than embryonal carcinomas (MTU, MTA), for teratomas are regarded as highly resistant to irradiation.

The above observations seem to be corroborated by Tyrrell and Peckham (1976), who in their series saw metastases more frequently in association with undifferentiated tumours (27%) than with more differentiated neoplasms (7%).
Some 10-20% of patients in clinical stage I have either died or developed demonstrable metastases after three years. Patients in this group require, not so much re-irradiation as (in most cases) polychemotherapy. It should be realized that in these cases the results of chemotherapy are less good, and that this therapy entails a graver risk, when radiotherapy has preceded (Stoter et al. 1979).

VI.6 Primary surgical treatment of patients with a non-seminomatous tumour of the testis in stage II

Only if retroperitoneal lymph node dissection has demonstrated retroperitoneal metastases and further clinical study has shown that no metastases are localized cranial to the diaphragm is the disease classified as stage II. As already indicated in chapter V, the three-stage classification of Boden and Gibb (1951) is too gross for clinical use. They include both the patient with a "bulky tumour" and the one with a small metastasis in a single lymph node in stage II. Patients of these two categories, however, differ in treatment required and in prognosis. This is why the extent of metastatic growth in stage II should be specified. In the following outline of therapy, an attempt will be made to do so.
As in stage I, there are controversial views on the treatment of patients in stage II. Views hardly differ, however, on the question whether retroperitoneal lymph node dissection should or should not be followed by adjuvant therapy. The discussion focuses more on the controversy "adjuvant chemotherapy or radiotherapy". In addition, the question whether unilateral dissection suffices and whether the lymph nodes cranial to the renal vascular pedicle should be removed, continues to play a role.
It was pointed out in chapter III that contralateral metastases are found in a large number of cases. Ray et al. (1974) reported 13% and 20% for the right and the left side, respectively. Hultén et al. (1973) found contralateral metastases in as many as 44% of cases with ipsilateral metastases. The studies of Walsh et al. (1971) and Johnson et al. (1976) revealed that there is no prognostic difference between unilateral and bilateral lymph node dissection in stage II either; but their studies give no information on the condition of the contralateral lymph nodes. On theoretical and clinical grounds,

bilateral or extended unilateral lymph node dissection is none the less to be preferred in stage II.

In our department, the renal vessels are accepted as demarcation of the cranial limit of dissection. This is in accordance with the views of Staubitz et al. (1974, 1979). As previously mentioned, patients with metastases cranial to the renal vascular pedicle are regarded as inoperable to begin with, and therefore given primary chemotherapy. Donohue et al. (1979) extend dissection to 4-6 cm cranial to the renal vascular pedicle. In seven out of 28 patients with metastases caudal to the renal vessels, they found suprahilar metastases as well. They therefore advocate extended suprahilar dissection, even going so far as to remove the contralateral para-iliac lymph nodes as well, if paralumbar metastases are found. There are no other publications on lymph node metastases cranial to the renal vascular pedicle, and it has not so far been established whether a cranialy extended dissection improves the prognosis (Fraley et al. 1979b; Donohue et al. 1978).

Only a few small series of patients in stage II were treated by retroperitoneal lymph node dissection alone. A survey is presented in table VI.6.

	3-year survival	5-year survival
Walsh et al. (1971)	3/4 (75%)	—
Castro (1969)	1/5 (20%)	—
Earle (1973)	10/17 (59%)	—
Staubitz et al. (1973)	15/20 (75%)	12/17 (70%)

Table VI.6: Non-seminomatous tumours of the testis stage II. 3-year and 5-year survival after retroperitoneal lymph node dissection alone.

There may have been some selection of these patients on the basis of operability, although no definite information is available. Recent literature no longer supplies data on the results of surgical treatment alone in stage II patients. It is generally accepted that surgery should be followed by further treatment: radiotherapy, chemotherapy or a combination of these two. It is therefore difficult to compare the various series. Moreover, the true efficacy of retroperitoneal lymph node dissection can hardly be determined accurately since the recent introduction of highly effective cytostatics. Whereas patients with "bulky disease" used to have a distinctly less favourable

prognosis, it is currently possible in many of these cases to perform radical dissection after treatment with several cytostatics (Comisarow and Grabstald 1976).
The various types of treatment will be separately discussed. Table VI.7 presents a survey of a few series of patients given radiotherapy after retroperitoneal lymph node dissection.

	3-year survival
Castro (1969)	10/17 (59%)
Walsh et al. (1973)	9/16 (56%)
Bradfield et al. (1973)	10/31 (32%)
Hussey et al. (1977)	13/26 (50%)

Table VI.7: Non-seminomatous tumours of the testis stage II. 3-year survival after retroperitoneal lymph node dissection followed by radiotherapy.

Only Hussey et al. (1977) reported their therapeutic results in relation to the extent of retroperitoneal metastatic growth. When at operation it was found that the lymphogram had been false negative, the 3-year survival was 65% (9/14). When the retroperitoneal lymph nodes were of "moderate size", the 3-year survival was 33% (4/12).
Castro (1969), Walsh et al. (1971) and Hussey et al. (1977) gave postoperative radiotherapy (megavoltage or cobalt) at a dosage of 4000-5000 rad (40-50 Gy) in 4-6 weeks. Bradfield et al. (1973) gave only 3000 rad (30 Gy) (orthovoltage) in the majority of their cases. In their series, local recurrence was found in 59% (10/17) of patients, who all received less than 3000 rad (30 Gy), but in only 5 of the 14 patients given more than 3000 rad (30 Gy). Retroperitoneal recurrence occurred in only three of the patients (11.5%) treated by Hussey et al. (1977), with simultaneous metastases elsewhere in two. Metastases outside the retroperitoneum developed in nine other patients.
In the above-mentioned series, mediastinum and supraclavicular lymph nodes were not routinely irradiated because, after retroperitoneal metastasis, further metastasis is largely extranodal and not to the mediastinal or supraclavicular lymph nodes. Hussey et al. (1977) found this in 42.2% of their stage II patients. The moderate results listed in table VI.7 contrast with the results reported by Fraley et al. (1976). Their series has not been included in

the table because they report only 2-year survival. In a series of 26 patients given postoperative radiotherapy of the retroperitoneum, mediastinum and supraclavicular nodes, the 2-year survival was 81%.

The so-called "sandwich" technique has already been discussed in the sections on therapy in stage I. This technique, too, has been used in a number of small series, listed in table VI.8.

	3-year survival
Earle (1973)	10/20 (50%)
Nicholson et al. (1974)	6/8 (75%)
Hussey et al. (1977)	4/10 (40%)
Maier and Mittemeyer (1977)	19/21 (81%)
Lynch et al. (1978)	4/6 (67%)

Table VI.8: Non-seminomatous tumours of the testis stage II. 3-year survival after retroperitoneal lymph node dissection and "sandwich" technique.

Only the study of Maier and Mittemeyer (1977) was prospective and randomized. The other arm of this study included 11 patients treated only by orchiectomy and subsequent radiotherapy. The 3-year survival in this group was 82%.

In all series except that of Hussey et al. (1977), the mediastinum and the supraclavicular lymph nodes were irradiated as well as the retroperitoneum, at a dosage of 4000 rad (40 Gy) in 3-4 weeks. Earle (1973) gave 4500-5000 rad (45-50 Gy) megavoltage irradiation, Maier and Mittemeyer (1977) gave megavoltage or ^{60}Co, and Lynch et al. (1978) and Nicholson et al. (1974) gave ^{60}Co irradiation only. The study reported by Lynch et al. (1978) was a continuation of that of Nicholson et al. (1974). From the same centre came a publication by Dijkhuizen et al. (1968), which has not been included in this survey. This group treated a total of 20 stage II patients by the so-called "sandwich" technique. The 3-year survival was 70% (14/20). Two patients in this group died as a result of the operation. Although the results can be described as good (see also table VI.3), the authors refrained from further use of the "sandwich" technique in favour of adjuvant chemotherapy. Only in cases with recurrent tumour growth or unresectable metastases is radiotherapy still given.

The Maier group (Klein and Mittemeyer 1977; Maier 1979), however, con-

tinued to advocate preoperative irradiation. On the basis of clinical staging, Klein and Mittemeyer (1977) found a significant diminution of histologically abnormal nodes and significantly improved therapeutic results in their own series and that of Hussey et al. (1977). In their own series, however, blind supraclavicular lymph node biopsy had been performed before admission to the study, and the authors do not specify the number of patients thus eliminated. Nor do they indicate whether there was any difference in result between the different histological tumour types. In the series reported by Lynch et al. (1978), the prognosis of embryonal carcinoma seems better. However, the various series are too small to warrant definite conclusions. A comparison of the results of retroperitoneal lymph node dissection alone with those of dissection combined with radiotherapy leads to the conclusion that adjuvant therapy is in any case a necessity. The "sandwich" technique seems superior to postoperative radiotherapy alone, although the results of the latter method as reported by Fraley et al. (1976) are not worse. Moreover, cases in which mediastinum and supraclavicular lymph nodes were included in irradiation seem to have a better prognosis than those in which only the retroperitoneum was irradiated.

It is a conspicuous fact that both Lynch et al. (1978) and Fraley et al. (1976) abandoned radiotherapy in favour of chemotherapy. Once radiotherapy is given, after all, both surgical intervention and chemotherapy are more dangerous and therefore often less effective.

Fraley et al. (1976) even went so far as to adopt an expectant attitude when fewer than four abnormal retroperitoneal lymph nodes were found and tumour markers were negative. This immediately introduces the next point of contention. While there is already an unmistakable trend in favour of postoperative chemotherapy instead of radiotherapy, the question also arises whether chemotherapy should always be given in stages IIA and IIB. Particularly now that a combination of diagnostic possibilities (roentgenography, echography, tumour marker assay) is available, an expectant attitude may be justifiable.

Dissection is often impossible in stage IIC, and in these cases chemotherapy seems to be the primary indication (Skinner 1977), although preoperative radiotherapy seems a reasonable alternative (Tyrrell and Peckham 1976).

VI.6.1 *Adjuvant chemotherapy in stage II*

In the following survey of adjuvant chemotherapy in stage II, no attempt at comprehensiveness is made. The cytostatics reviewed are precisely those

also used in our department, which in the literature also proved important in discussion.

Of the various cytostatic agents, antibiotics and metaphase inhibitors are found to be the most effective in the treatment of non-seminomatous tumours of the testis. Little information is available on the effect of alkylating agents on tumours in this group. Nor have large series of patients been described who had been treated with antimetabolites like methotrexate and 5-fluoro-uracil (Carter and Wasserman 1975; Jacobs and Muggia 1980). In recent years, however, many reports have been published on the effect of cis-diammindichloroplatinum (cis-platinum, DDP).

Actinomycin-D, mithramycin, bleomycin and adriamycin are the most widely studied cytostatic antibiotics. A review of the literature on the efficacy of the separate agents by Jacobs and Muggia (1980) shows that the overall response rate of actinomycin-D is 33%, the complete remission rate being 18%. The corresponding figures for mithramycin are 37% and 9%, for bleomycin 43% and 11%, for adriamycin 17% and 0%, respectively. Vinblastine, which is also frequently used in the treatment of non-seminomatous testicular tumours, proved to have an overall response rate of 37% and a complete remission rate of 12%. Cis-platinum as single agent caused remission in 60% of cases, and complete remission in 19%.

Since Li et al. (1960) described the results obtained with a combination of chlorambucil, methotrexate and actinomycin-D (triple therapy), the above-mentioned agents have been frequently used in combination. The advantage of combination chemotherapy lies in the synergistic effect, because the sites of action on the cell differ. Moreover, the different cell types differ in sensitivity to the different agents.

The literature supplies but little information on adjuvant chemotherapy in stage II. Adjuvant therapy in stage II has developed in response to the ever better results obtained with cytostatics in the treatment of patients in stage III. After all, micrometastases can be expected to respond to cytostatics when macroscopic metastases show regression in response to this therapy. Although the sites at which distant metastases develop are not accurately known, it is generally assumed that the lungs are the site of predilection. Regularly, however, metastases are found also in the mediastinum and the supraclavicular lymph nodes (Whitmore 1970; Quivey et al. 1977).

As already mentioned, some 20-25% of patients in pathological stage II ultimately develop distant metastases despite treatment by postoperative

radiotherapy. This is why adjuvant chemotherapy is to be preferred to postoperative irradiation. The experience gained with adjuvant chemotherapy is based solely on non-randomized and retrospective studies, and consequently it has not been established which cytostatic agents or combinations give the best results. Nor has the maximally effective dose been determined. Nor has it been established whether adjuvant chemotherapy is indicated in cases of minimal disease (generally defined as lymph nodes smaller than 2 cm and numbering fewer than six).

	lung metastases	3-year survival
Merrin and Murphy (1974)	3/9 (37%)	8/9 (98%)
Williams et al. (1979)	15/31 (48%)	30/31 (97%)
Edson (1979)	unknown	15/20 (75%)

Table VI.9: Non-seminomatous tumours of the testis stage II. Development of lung metastases after retroperitoneal lymph node dissection followed by adjuvant actinomycin-D as a single agent.

The most widely used cytostatic agents are actinomycin-D (Merrin and Murphy 1974; Höffken et al. 1976; Schraffordt Koops et al. 1978; Williams et al. 1979; Edson 1979; Skinner 1980) or a combination of vinblastine,

Merrin and Murphy (1974)	
Actinomycin-D	0.5 mg i.v. daily × 5 days every 6-8 weeks.
Edson (1979)	
Actinomycin-D	15 μg/kg i.v. daily × 4-5 days preoperatively. after dissection same dosis each month for 4 months, then once per month for 6 months, then once every 3 months for a minimum of 2 years.
Einhorn and Donohue (1979a).	
Cisplatinum	20 mg/m² i.v. (during 15 min) daily for 5 days, once every 3 weeks for 4 courses.
Bleomycin	30 units i.v. weekly for 12 weeks.
Vinblastine	0.3 mg/kg i.v. daily for 2 days every 3 weeks for 4 courses. — Vinblastine given 6 hr prior to Bleomycin. — Saline hydration started at least 12 hr prior to Cisplatinum and continued throughout 5 days course of Cisplatinum at rate of 100 cc/hr normal saline. — Maintenance Vinblastine (0.3 mg/kg every 4 weeks) started after completion of Bleomycin and continued for 2 years.

Vugrin et al. (1979).

Mini-VAB.	Vinblastine i.v.	0.6 mg/kg	q wk × 6
	Actinomycin-D i.v.	0.02 mg/kg	
	Bleomycin i.v.	0.25 mg/kg	
	2 wk interval		
	Actinomycin-D i.v.	0.02 mg/kg	q 14 days
	Chlorambucil p.o.	0.1 mg × 7 days	for 1 year.
	followed by		
	Actinomycin-D i.v.	0.02 mg/kg	q 21 days
	Chlorambucil p.o.	0.1 mg × 7 days	for 1 year

Samuels et al. (1979a).

VB_1	Vinblastine 0.4 mg/kg total dose days 1 and 2.
	Bleomycin 30 units i.m. twice weekly × 10 weeks.
VB_2	Vinblastine 0.4 mg/kg days 5 and 6.
	Bleomycin 30 units per liter normal saline over 24 hr × 5 days.
VB_3	Vinblastine 0.4-0.6 mg/kg days 1 and 2.
	Bleomycin 30 units per liter normal saline over 34 hr × 5 days (days 5 through 6).
Bleomycin-COMF	Bleomycin 30 units i.m. twice weekly × 4 weeks.
	Cyclophosfamide 200 mg/m² i.v. daily × 4 weeks.
	Vincristine 2.0 mg i.v. days 1 and 7.
	Methotrexate 15 mg/m² twice weekly × 4 weeks.
	5-fluorouracil 400 mg/m² i.v. daily days 1 and 5.

Golbey et al. (1979).

VAB III.	Day 1-7	Cyclophosphamide	600 mg/m² i.v.
		Vinblastine	4 mg/m² i.v.
		Actinomycin-D	1 mg/m² i.v.
	Day 1-7	Bleomycin	20 mg/m² continuous infusion × 7 days
	Day 8	Cisplatinum	120 mg/m² i.v. with mannitol induced diuresis.
	Consolidation: treatment every 3 weeks		
Treatment 1 and 4		Vinblastine	4 mg/m² i.v.
		Adriamycin	30 mg/m² i.v.
		Chlorambucil	4 mg/m² p.o./day × 14 days.
Treatment 2 and 5		Vinblastine	4 mg/m² i.v.
		Actinomycin-D	1 mg/m² i.v.
		Chlorambucil	4 mg/m² p.o./day × 14 days.
Treatment 3 and 6		Vinblastine	4 mg/m² i.v.
		Cisplatinum	50 mg/m² i.v.
		Chlorambucil	4 mg/m² p.o./day × 14 days.
	Reinduction: same as induction		
	Maintenance: every 3 wk for 2 yr:		
		Vinblastine	4 mg/m² i.v.
		Actinomycin-D	1 mg/m² i.v.
		Chlorambucil	4 mg/m² p.o./day × 14 days.

Table VI.10: Survey of some chemotherapeutic regimens as described in chapter VI.

actinomycin-D and bleomycin (Vugrin et al. 1979; Golbey 1979) or of vinblastine and bleomycin (Samuels et al. 1979b) (table VI.10).

Table VI.9 presents a survey of some series of stage II patients given postoperative actinomycin-D. The extent of retroperitoneal metastatic growth is not specified.

Of the nine patients described by Merrin and Murphy (1974), three developed pulmonary metastases despite actinomycin-D. In all these cases these metastases could be surgically removed. The actinomycin-D dosage ranged from 0.5 mg to 1 mg per day during 5 days, usually given every other six weeks. The total duration of treatment was generally 2 years. Skinner (1979) and Edson (1979) start treatment even before retroperitoneal lymph node dissection, even if no metastases are found (although Skinner confines administration to a brief period in that case). There is no information on the precise method used for the administration of actinomycin-D; it is unknown whether the daily dose was given in a single intravenous injection or by continuous drip over several hours.

Of the 31 patients described by Williams et al. (1980), 30 survived after polychemotherapy (cis-platinum, vinblastine and bleomycin), alone or in combination with adriamycin (PVB + adr.). In view of the good results of PVB treatment, Williams et al. (1979) gave no further adjuvant chemotherapy after radical dissection in stage II. PVB treatment, alone or in combination with adriamycin, was given only when metastases became manifest in the course of the careful follow-up. So far, these authors have achieved complete remission in all cases.

Vugrin et al. (1979) treated a series of 62 stage II patients with a combination of vinblastine, actinomycin-D and bleomycin in doses smaller than those used in stage III (mini-VAB). In this group, 33 patients had fewer than 5 positive lymph nodes which, moreover, were smaller than 2 cm and showed no ingrowth in adjacent tissues. The tumour markers were negative. The minimum follow-up period was 19 months. The 33 patients all survived without demonstrable metastases. The other 29 patients showed more extensive retroperitoneal lesions; they were treated by the VAB III programme, which includes cis-platinum and chlorambucil, because it was found that metastases frequently developed despite mini-VAB treatment. Ultimately, 19 of these 29 patients (65%) were without metastases during a minimum of 25 months. These authors, too, concluded from their retrospective study that no adjuvant chemotherapy is required in patients with minimal disease.

Samuels et al. (1979) gave vinblastine and bleomycin (VB) as adjuvant treatment. Their study was retrospective. The series consisted of 27 stage II patients, including 21 with extensive metastases. Use was made of the VB_1, the VB_3 and the bleomycin-COMF programme. Of the 27 patients, three died (11%); two of these had been given VB_1 treatment. It is to be mentioned that a few cases of bulky tumour were given radiotherapy as well. One of the three deceased patients died as a result of radiation enteritis! In view of the good results obtained with VB alone, these authors hold that cis-platinum is not required as an adjuvant drug in stage II and is in fact better to be avoided in view of toxic effects on kidneys and hearing.

Comparing the results obtained with adjuvant chemotherapy in stage II with those of adjuvant radiotherapy, one finds that at first sight the results seem better when postoperative chemotherapy is given. However, it is uncertain whether the various series can in fact be compared. Moreover, some centres treat bulky disease by chemotherapy and radiotherapy.
As already pointed out, there is a tendency to refrain from adjuvant therapy in minimal disease. The risk of watchful waiting can be accepted now because highly effective combinations of cytostatics are available. In the case of metastasis a remission can still be achieved. However, a more prolonged follow-up will have to show whether an expectant attitude is realy justifiable. Skinner and Scardino (1980) recently demonstrated that, precisely in cases of minimal disease, the rate of false negative tumour marker assays was 50%. This means that tumour markers are not always reliable parameters during the development of (micro)metastases.

VI.6.2 *Preoperative chemotherapy*

It is not always possible to perform lymph node dissection. The node metastases can be so extensive that the procedure is not technically feasible because the nodes are all fixed to the aorta, inferior vena cava and renal vessels. Publications by Comisarow and Grabstald (1976), Skinner (1977b), Hong et al. (1977), Schraffordt Koops et al. (1978) and Merrin (1980) show that the prognosis in patients of this group need not be exceedingly poor. Regression of the metastases was always achieved after chemotherapy (vinblastine, bleomycin, actinomycin-D and cis-platinum), sometimes combined with radiotherapy. Laparotomy revealed that the remaining tumour consisted of fibrotic tissue and necrosis or "mature teratoma". It was generally possible to remove the remnants of the metastases. A combination of the

above-mentioned cytostatics had been used in all cases. There are no publications on similar results obtained with the individual agents.
The mechanism by which metastases of a non-seminomatous testicular tumour evolve to "mature teratoma" has so far remained obscure. Hong et al. (1977) and Oosterhuis et al. (1980) mention three possibilities in this context: 1) treatment destroys the malignant cell, whereupon the well-differentiated cells persist; 2) treatment may induce the evolution of malignant cells to more highly differentiated tissue; 3) malignant cells are capable of spontaneous differentiation. Since the therapy increases the total duration of illness the tumour has an opportunity to undergo this evolution. The finding of "mature teratoma" tissue is probably less favourable prognostically than a complete remission; pertinent data, however, are not yet available.
As already mentioned in the discussion of patients in stage I, the treatment of some histological types seems less successful than that of others. Embryonal carcinoma, for example, seems to have a less favourable prognosis than teratocarcinoma. The series of patients listed in table VI.4 are too small to warrant conclusions for stage II. Differences in therapeutic results between the two tumour groups, if any, cannot be traced in the recent publications of Skinner (1976a, 1977a), Lynch et al. (1978) and Donohue et al. (1979). Perhaps this is due precisely to adjuvant chemotherapy. Samuels et al. (1979) obtained very favourable therapeutic results with vinblastine/bleomycin combinations, especially in embryonal carcinoma and in cases with small metastases.

VI.7 Primary radiotherapy in the treatment of patients in clinical stage II

Clinical stage II prevails when all the available diagnostic methods show that the tumour has spread to the retroperitoneum but not outside it (even though this is not histologically confirmed).
Lymphography is the technique most widely used in the diagnosis of retroperitoneal lymph node lesions. In addition, the CT-scan and echography are now being used. As mentioned in chapter IV, the reliability of lymphography is not 100%. False negative findings are fairly common, but false positive findings are obtained in 59-100% of cases according to the literature (see table VI.1). We may assume that the lymphogram is erroneously interpreted as positive in 10-15% of patients. This implies that these patients receive excessive therapy which is not commensurate with the stage of the disease.

As in clinical stage I, it proved difficult in clinical stage II to compare the results of therapy with those in pathological stage II. A survey will be presented of the primary radiotherapeutic treatment of patients in clinical stage II.

These patients generally receive 4000-5000 rad (40-50 Gy) in 4-6 weeks, the dosage varying from centre to centre. The mediastinum and supraclavicular lymph nodes are as a rule routinely included in irradiation with 4000 rad (40 Gy) in 4-5 weeks. Only on the series of Castro (1969) and Blandy et al. (1976) are no data available in this respect. Table VI.11 presents a survey of a few series of patients given only radiotherapy after orchiectomy. The 3-year survival ranges from 0% to 82%.

	3-year survival	5-year survival
Castro (1969)	0/5 (0%)	—
Tyrrell and Peckham (1975)	17/29 (59%)	—
v.d. Werf-Messing (1976)	16/35 (45%)	idem
Blandy et al. (1976)	5/20 (25%)	4/20 (20%)
Maier and Mittemeyer (1977)	9/11 (82%)	—
Tierie et al. (1979)	9/20 (44%)	—

Table VI.11: Non-seminomatous tumours of the testis clinical stage II. 3-year and 5-year survival after orchiectomy and radiotherapy.

The series of Van der Werf-Messing (1976) consisted of patients in clinical stage N_1 (positive lymphogram, no palpable intra-abdominal tumour), while that of Tierie et al. (1979) comprised both stage N_1 and N_2 (palpable intra-abdominal tumour). The 3-year survival was 54% (7/13) stage N_1 and 28.5% (2/7) in stage N_2.

Tyrrell and Peckham (1975) reported a retrospective study of the lymphograms in their series, concluding that 12/14 (86%) of the patients with metastases smaller than 2 cm survived 3 years, versus only 5/15 (33%) of those with metastases larger than 2 cm. Seven patients in this series were afterwards treated by retroperitoneal lymph node dissection because the tumour had failed to disappear after radiotherapy. Blandy et al. (1976) likewise resorted to surgery for removal of residual lymph node metastases in a few cases.

The stage II patients with MTIA (now known as MTI) in the series of Van der Werf-Messing (1976) had a better prognosis than those with MTA (now known as MTU). The 5-year survival was 75% in the MTIA group, versus

35% in the MTA group. The series of Blandy et al. (1976) also shows this difference in favour of MTI.

Although most authors do not differentiate between limited and more extensive lymphographic changes, the series of Tyrrell and Peckham (1976) seems to indicate a limit, above which radiotherapy is less effective. As a follow-up on the paper published by Tyrrell and Peckham (1975), Hendry et al. (1980) recently reported the results of more differentiated therapy. They subdivided clinical stage II on the basis of the size of lymph node metastases: stage IIA (maximum diameter 2 cm), stage IIB (diameter 2-5 cm), and stage IIC (diameter in excess of 5 cm).

The size of the lymph node metastases was determined with the aid of lymphography, echography and CT-scan. These authors proceeded from the postulate that patients in stage IIA can equally well be treated by radiotherapy as by retroperitoneal lymph node dissection. In stages IIB and IIC, chemotherapy alone or in combination with radiotherapy can effect a degree of regression which leaves only remnants of metastases for surgical removal. The operation was performed six weeks after chemotherapy. Although the follow-up was short, 12 of the 13 patients survived after combined chemotherapy and radiotherapy. One patient died as a result of the operation.

This approach in fact corresponds with that of the advocates of retroperitoneal lymph node dissection. In this context the question arises whether treatment in stages IIB and IIC should in fact be primarily chemo- and radiotherapeutic with surgery as adjuvant treatment, or whether treatment in stage IIB should be primary laparotomy/retroperitoneal lymph node dissection, followed by chemotherapy. Should laparotomy reveal stage IIC, chemotherapy can first be given, after which node dissection is as a rule feasible.

The treatment of clinical and pathological stage IIA is still a major subject of discussion. The therapeutic results reported by Peckham (1979) correspond with those of surgical treatment. The 2-year survival of 28 patients in clinical stages I and IIA was 100%. Three patients who developed metastases, showed complete remission after chemotherapy.

A study of the results of Peckham (1979) and Hendry et al. (1980) raises the question whether radiotherapy alone still has a place in the treatment of stages IIB and IIC. It should again be pointed out that both chemotherapy and radiotherapy of the retroperitoneal lymph node sites produce more complications. Particularly in stages IIB and IIC these can constitute a major problem. We therefore believe that radiotherapy should be refrained from in

these cases. The therapy of choice in stages I and IIA can only be determined in a prospective and randomized study. Uniformity in staging and histological classification is a prerequisite for this. In our opinion, these cases too should not be given radiotherapy when adequate surgical and chemotherapeutic possibilities exist.

CHAPTER VII

OPERATIVE TECHNIQUES AND COMPLICATIONS

VII.1 Introduction

The surgical treatment of testicular tumours begins with exploration of the affected testicle, proceeding from the postulate that any change of the testicle is malignant until proven to be otherwise.

The exploration is preceded by general haematological studies and analysis of the urine, and determination of the HCG and AFP values. A plain chest X-ray is also routinely obtained.

The only proper approach to the affected testicle is via an inguinal incision. Biopsy, needle biopsy or orchiectomy via the scrotum are technical errors because the scrotum is contaminated with tumour cells in this way. Moreover, tumour tissue can be left behind in the spermatic cord. Markland et al. (1973) found residual tumour tissue or tumour recurrence in six of a series of 19 patients so treated.

Post and Belis (1980) found inguinal node metastases in five of six patients whose scrotum was contaminated. The chance of a cure of a patient with a malignant testicular tumour is reduced by contamination with or persistence of tumour tissue, and surgical treatment always has to be expanded. The scrotum, after all, drains not to the retroperitoneal but to the inguinal lymph nodes. Consequently, these cases require hemiscrotectomy and inguinal lymph node dissection when the growth is a non-seminomatous testicular tumour, or irradiation of this area when the tumour is a pure seminoma.

VII.2 Orchiectomy

The approach to the inguinal canal is the same as that in operations for inguinal hernia. The aponeurosis of the external oblique muscle is divided

parallel to the course of the fibres. The spermatic cord is then dissected free, mobilized and clamped off as far cranially as possible with a rubber ligature to minimize the risk of tumour embolism.
Next, the spermatic cord is dissected free further in the direction of the scrotum, whereupon the testicle can generally be lifted from the scrotum without difficulty for inspection and palpation. In the case of doubt, frozen sections of a tumour biopsy specimen can be examined, always taking care to avoid contamination of the wound. When the tumour proves to be malignant, vessels and ductus deferens are separately ligated at the highest possible level. Testicle and spermatic cord can then be resected. If the tumour is to be examined by enzymatic histochemical techniques, the resected specimen should be taken to the pathologist in melting ice, without fixation.

VII.3 Retroperitoneal lymph node dissection

Our department has opted in favour of transabdominal bilateral retroperitoneal lymph node dissection for the treatment of patients with a non-seminomatous testicular tumour. We accept the renal vascular pedicle as cranial boundary. Some authors have described the extraperitoneal thoraco-abdominal approach, which will be discussed later.
Our department prefers the transabdominal approach because it has theoretical as well as practical advantages over the thoraco-abdominal procedure. The principal advantage is that extensive contralateral lymph node dissection can be carried out, and that contralateral para-iliac lymph nodes can be removed as well. The extraperitoneal thoraco-abdominal approach does not permit so extensive a dissection. Given a right-sided tumour, the nodes caudal to the left inferior mesenteric artery cannot be removed in that approach. Given a left-sided tumour, the dissection on the right can be extended as far as the site at which the left spermatic vein enters the inferior vena cava (Skinner 1976a).
Contralateral metastatic spread is often found. Staubitz et al. (1974) observed it in over 30% of their patients, and Hultén et al. (1973) in as many as 44%. These figures seem to provide an important argument in favour of transabdominal bilateral retroperitoneal lymph node dissection.
The advocates of the thoraco-abdominal approach remove the lymph nodes cranial to the renal hilus as well. Fraley (1977) even removes the ipsilateral adrenal gland. The argument that suprahilar lymph nodes can only be removed via a thoraco-abdominal incision has been repudiated and dis-

proved by Donohue (1977), in whose department more than 100 patients were treated by high bilateral retroperitoneal lymph node dissection via the transabdominal route.

Another advantage of the transabdominal approach is that intra-abdominal organs like the liver and the mesentery of the small intestine can also be inspected for the presence of metastases. Fraley (1977), as advocate of the thoraco-abdominal approach, held that postoperative recovery is accelerated when the peritoneum is not opened. In our opinion the manipulation of intra-abdominal organs hardly, if at all, prolongs the intestinal paralysis resulting from the retroperitoneal operation. Skinner (1977b), likewise an advocate of the thoraco-abdominal approach, always opens the peritoneum for inspection of the abdominal organs.

A third advantage of the transabdominal approach to the retroperitoneum is that the procedure takes far less time than the thoraco-abdominal operation as long as it is confined to levels caudal to the renal hilus (Fraley 1977).

A disadvantage of the transabdominal approach lies in the possibility of postoperative adhesions. In the event of postoperative radiotherapy, local damage to the intestine may be more extensive in that case due to reduced intestinal motility. With the increasing use of adjuvant chemotherapy and abolition of postoperative radiotherapy, however, this problem is losing importance (Lindsey and Glenn 1976; Fraley 1977).

In the thoraco-abdominal approach, in which contralateral lymph nodes are less adequately removed, the contralateral sympathetic trunk remains intact over a longer distance so that ejaculation disorders are reputedly less frequent. This too, however, has been repudiated by others (Kedia et al. 1977).

Staubitz et al. (1974) maintained that the young patient should be given the best possible chance of a cure. This implies that extensive bilateral lymph node dissection is required. No compromise can be accepted between maintenance of antegrade ejaculation and non-radical resection of tumour tissue.

In the form in which it is performed for non-seminomatous testicular tumours, retroperitoneal lymph node dissection is also carried out in the treatment of malignant tumours arising from the spermatic cord (e.g. embryonal rhabdomyosarcoma), because the lymph drainage pattern is identical to that of the testis (Maurer et al. 1977; Hoekstra et al. 1980).

VII.3.1 *Technique of transabdominal bilateral retroperitoneal lymph node dissection*

The patient receives a liquid diet for one day preoperatively to ensure a more

or less empty bowel. An enema is routinely given. No other preoperative measures are required. In the course of the years, the experience gained has dictated a personal technique which does not differ essentially from that described by other authors (Stehlin et al. 1959; Staubitz et al. 1973; Johnson et al. 1976).

After introduction of anaesthesia an urinary catheter is inserted to supply information on urine production during the operation. Moreover, it ensures collapse of the bladder and thus facilitates operation in the true pelvis.

The patient is placed supine on the table. The skin is desinfected with a solution of iodine in alcohol, and so draped that the incision can extend from the xiphoid process to the symphysis pubis. One generally starts with a lower abdominal midline incision, followed by palpation of the abdomen to ascertain whether retroperitoneal metastases are present and, if so, whether they can be removed. The liver is palpated as well.

When this exploration shows that the retroperitoneal lymph nodes can be removed, the incision is extended to the symphysis pubis and the xiphoid process. A large abdominal wall retractor is inserted. Via a nasal tube it has been ensured that the stomach contains no air. The small intestine is now moved craniadly to expose the retroperitoneum. Next, caecum and ascending colon are moved to the midline and dissected free along the white line in the right paracolic sulcus. The parietal peritoneum can now be mobilized without difficulty in an avascular plane. On the medial side, the retroperitoneum is then incised along the edge of the mesenteric root between the ligament of Treitz and the inferior mesenteric vein. This makes it possible to move the entire caecum, ascending colon and mesentery in cranial direction. Some mobilization of the duodenum is usually required. In the case of a left-sided tumour, the descending colon sometimes has to be mobilized for adequate exposure of the retroperitoneum.

Dissection is usually started on the right. The first step is to lift the strand of the spermatic cord from the internal inguinal ring and to mobilize it craniadly. The ductus deferens is divided and ligated as close to the bladder as possible. After identification of the right ureter the adipose tissue is dissected free from the iliopsoas muscle and from the lower pole of the kidney in median direction. The ureter is carefully lifted, whereupon the adipose tissue localized dorsal to it can be dissected free from the underlying structure in median direction, as far as the inferior vena cava.

With a left-sided primary tumour, only the adipose tissue medial to the lower pole is removed; with a right-sided tumour, all adipose tissue sur-

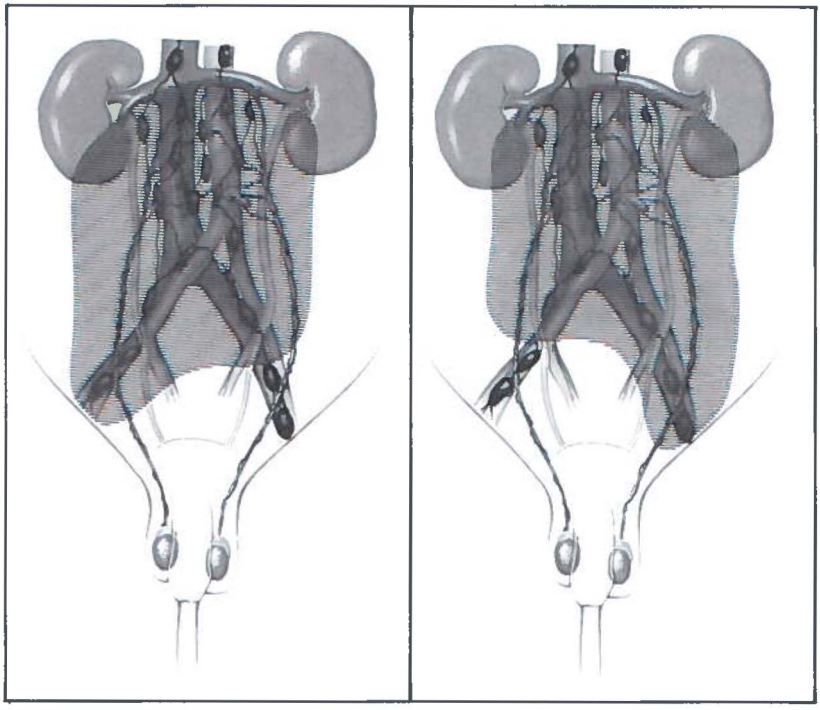


Fig. VII.1 Areas of dissection for right-sided and left-sided tumour.

rounding the lower pole is removed along with the specimen resected. The glandular and adipose tissue medial to the lower pole of the kidney comprises the primary lymph node sites. This tissue is dissected free from the underlying structure in the direction of the inferior caval vein, keeping the right renal vein in view as cranial boundary. It is generally not too difficult to dissect the tissue which surrounds the inferior caval vein. At the same time, the right spermatic vein is ligated at its site of entry and divided. This is done in left-sided as well as in right-sided tumour localization.

Next, the left renal vein is identified and dissection on the left is started, again with the renal vein as cranial boundary. Dissecting across the aorta, the tissue localized caudal to it is dissected free. The left spermatic vein is ligated and divided and perirenal adipose tissue is removed, entirely or partly, dependent on the localization of the primary tumour. More caudadly, the lateral edge of the iliopsoas muscle is identified, and subsequently the ureter. All adipose and glandular tissue is dissected free from underlying structures in medial direction, loosening the ureter from its bed.

High up between the aorta and the inferior vena cava, the cisterna chyli is identified, ligated with the aid of a haemo-clip, and divided. However, the cisterna chyli is not always found at this level; in some cases it is localized more cranial. The tissue between and ventral to the two large vessels is dissected free from the vertebral column in caudal direction, en bloc with the already dissected adipose and glandular tissue on either side of the vessels. In some cases this cannot be done without dividing lumbar vessels.
The left spermatic artery is ligated near its origin and divided. More caudadly, the inferior mesenteric artery is ligated and divided at its origin but not until it has been temporalyclamped to establish whether circulatory changes develop in the descending colon and sigmoid.
Dissection is continued para-iliacally as far as the internal iliac artery. This cannot be done unless the mesosigmoid is divided after mobilization of the sigmoid on the left. Dependent on the localization of the primary tumour, the glandular tissue along the external iliac artery is likewise removed, as far as Poupart's ligament. This completes dissection (fig. VII.2).
The adipose and glandular tissue localized medial to the two kidneys, which comprises the primary lymph node sites, is marked for microscopic examination by the pathologist.
The abdominal cavity is irrigated with physiological saline solution and vessels still found bleeding are coagulated. Finally, a plain abdominal X-ray is obtained to establish whether the dissection has removed all lymph nodes containing contrast medium. Nodes still found in situ, if any, are extirpated.
The retroperitoneum is reperitonealized along the mesenteric root and, if the dissection on the left has extended along the external iliac artery, the mesosigmoid is closed. Elective appendectomy is then performed, whereupon the abdominal wall is closed in layers.

VII.3.2 *Technique of thoraco-abdominal retroperitoneal lymph node dissection*

Although thoraco-abdominal retroperitoneal lymph node dissection has not been performed in our department in the past several years, the technique of this operation is nevertheless described because the first patient was so treated. The procedure has been described by Cooper et al. (1950) and Leadbetter (1953).
The patient is placed on the table in lateral recumbent position, with the body tilted slightly back. The lumbar vertebral column is given the same curvature as for a renal operation.

Fig. VII.2 Review of the retroperitoneum after the dissection is completed.

The skin incision is made from the posterior axillary line via the tenth rib to the point between the internal inguinal ring and the lateral margin of the rectus abdominis muscle. The tenth rib is subperiosteally resected, and the musculature of the abdominal wall is sharply divided. The pleural cavity is then opened and the diaphragm incised in dorsolateral direction. The peritoneum can now be mobilized to expose the retroperitoneum from the diaphragm down. The retroperitoneum is then palpated to assess operability.

Dissection starts cranially from the crus of the diaphragm and ends at the internal inguinal ring. The perirenal adipose tissue is dissected free from the kidney, and the same is done with glandular and adipose tissue cranial, dorsal and ventral to the renal vascular pedicle. The spermatic vessels are ligated and divided. Early identification of the ureter is important. In dissection on the left, the adipose and glandular tissue localized lateral and ventral to the aorta is removed; in dissection on the right, the adipose and glandular tissue lateral and ventral to the inferior vena cava is removed.

In dissection on the left, the inferior mesenteric artery is left intact. It is often possible to remove the retro-aortic and retrocaval nodes as well.

The dissection extends caudadly along the common iliac artery and the external iliac artery as far as the internal inguinal ring. The thorax is closed over a drain. The wound is closed in layers. Before completing the operation it is advisable to obtain a chest X-ray to ascertain whether the lung has expanded properly.

The above described technique is no longer being applied in this form because it does not leave enough room for exploration of the contralateral side. Cooper et al. (1950) described a number of patients who required a bilateral operation because palpation revealed the presence of metastases on the contralateral side as well. By extending the incision, the contralateral renal hilus can be reached, and dissection of this area can be performed (Skinner 1976a, Fraley et al. 1977; Catalona and Rubenstein 1978). Another limitation of this method, as already explained, is that the more caudal contralateral lumbar lymph nodes can be removed only with difficulty, if at all.

VII.3.3 *Efficacy of retroperitoneal lymph node dissection*

In an attempt to establish how many lymph nodes can be removed at retroperitoneal node dissection, Tavel et al. (1963) performed transabdominal

bilateral retroperitoneal lymph node dissection on cadavers. They found that, at best, only 76% of the lymph nodes in the primary drainage region were removed. Opponents of primary surgery in the treatment of non-seminomatous testicular tumours regularly refer to this study.
In 1976, however, Kaswick et al. carried out a similar study, but they ligated the lumbar arteries and veins as well, so that aorta and inferior vena cava could be mobilized completely. This made it possible to remove all adipose and glandular tissue ventral to the vertebral column. Unlike Tavel et al. (1963), these authors found no lymph nodes left in situ after the operation. They demonstrated that retroperitoneal lymph node dissection can certainly be effective, provided the nodes localized between the large vessels and the vertebral column are removed as well.
Allhoff et al. (1981) recently described nuclide detector-guided lymph node dissection. During lymphography they labelled the lymphoid tissue with ^{198}Au colloid, so that at retroperitoneal lymph node dissection shortly afterwards, all lymphoid tissue could be identified with the aid of a detector and removed.

VII.4 Complications of retroperitoneal lymph node dissection

In view of the extensive surgery it is not surprising that complications can develop. The literature reports complication rates ranging from 6.9% to 30% (Staubitz et al. 1974; Johnson et al. 1976; Lindsey and Glenn 1978; Sago et al. 1979). The complications can be divided into three groups: 1) peroperative complications, 2) postoperative complications, and 3) ejaculation disorders.

VII.4.1 *Peroperative complications*

One of the most serious complications is damage to one of the ureters. Severance of this structure during dissection in the para-iliac area is notorious. Reimplantation of the ureter is possible in such cases. After severance at a more cranial level, reanastomosis is more difficult because skeletization during dissection may have compromised the vascularization of the ureter. In such cases Skinner (1976b) recommends - at least if the other kidney is intact - to resect the kidney on the affected side or to reimplant it, as in kidney transplantation.
At dissection near the caudal pole of the kidneys, one of the arteries of the caudal pole may be damaged. When this is a small artery, this has no very serious consequences. And since the large arteries can always be identified,

they are rarely damaged. Beck and Stutzman (1979), however, described a patient in whom the renal artery was accidentally clamped off with a haemoclip, resulting in subsequent hypertension and even a cerebrovascular accident.
Ligation of the inferior mesenteric artery can lead to ischaemia of the colon. It is important, before definitively ligating this vessel, to place a clamp temporarily to see whether the circulation of the descending colon and the sigmoid is adequate. Because most of the patients are young the problem will rarely arise. However in patients over 45 years of age there is certainly a risk of ischaemia. Skinner (1976b) described transient diarrhoea as a result of this ischaemia.
At dissection in the area around aorta and vena cava, lumbar arteries and veins may be damaged. Haemostasis is as a rule readily achieved with the aid of a haemoclip. In some cases it may be necessary to sacrifice a few lumbar arteries and veins for the sake of adequate dissection. This makes it possible to remove nodes localized dorsal to these vessels. Devascularization of the spinal cord as a result of ligation of the lumbar arteries has not been described after retroperitoneal lymph node dissection. Whenever the great radicular artery (Adamkiewicz) arises at a lumbar level, there is always a major collateral artery from the thoracic aorta (Adams and Van Geertruyden 1956; Coupland and Reeves 1968). This collateral circulation ensures adequate vascularization of the spinal cord after ligation of lumbar arteries.

VII.4.2 *Postoperative complications*

Postoperative complications after retroperitoneal lymph node dissection are divided into two groups: 1) complications of the type which can develop after any laparotomy; 2) more or less specific complications of retroperitoneal lymph node dissection.

VII.4.2.1 General complications

General complications of retroperitoneal lymph node dissection include: postoperative haemorrhage, pneumonia, thrombo-embolism, urinary infection and disturbed wound healing.
Staubitz et al. (1974) reported one instance of postoperative haemorrhage in a group of 65 patients; Sago et al. (1979) reported the same in two out of a group of 47.
Pneumonia can nearly always be prevented be aimed measures such as preoperative and postoperative physiotherapy.

Thrombo-embolic processes are rare as long as adequate anticoagulant medication is routinely given; in our department we use coumarol derivatives for this purpose.
Urinary infections may develop because a urinary catheter is always introduced prior to operation. In our department, removal of the catheter is routinely followed by administration of a sulpha-drug, and measures are taken to ensure ample diuresis. Always, moreover, a sample of urine is taken after removal of the catheter for culture. Whenever pathogenic microorganisms are found in the culture, antibiotics or chemotherapeutics are given on the basis of the antibiogram.
Disturbed wound healing is a possibility because the vitality of the wound edges is reduced by transient ischaemia resulting from the use of the abdominal wall retractor and the long duration of the operation. Staubitz et al. (1973) reported one instance of wound infection and one of wound dehiscence in a series of 65 transabdominal retroperitoneal lymph node dissections. One other patient showed a persistent wound fistula. A cicatricial hernia was seen in one case. Lindsey and Glenn (1976) found wound dehiscence in one out of 66 patients, and Sago et al. (1979) reported two cases in a group of 47. It is of interest to note the latter authors' observation that disturbed wound healing occurred in some 25% of patients whose operation had included an appendectomy, as compared with 9.5% of those were the appendix was not removed.

VII.4.2.2 Specific postoperative complications

Although chylous ascites cannot be regarded as a true complication of retroperitoneal lymph node dissection, it is nevertheless a condition which may result precisely from this type of operation. The condition is caused by damage to the retroperitoneal lymph node plexus, and as a rule can be observed within three days after the operation. It seems likely that sufficient collateral lymphatics remain for ultimate drainage of the lymph from intestine and leg, for the ascites nearly always disappears spontaneously. In some cases, however, a retroperitoneal lymph cyst forms as described by Guinn (1976); this is due to retroperitoneal lymph accumulation.
It is difficult to explain the chylothorax described by Beck and Stutzman (1979) as complication of a dissection extended cranial to the renal hilus. Another complication reported was internal herniation of the small intestine dorsal to the common iliac artery (Guba et al. 1978); its cause was undoubtedly non-reperitonealization of the mobilized artery.

Walsh et al. (1971) reported haemorrhagic necrosis of the aorta, requiring implantation of a bifurcation prosthesis. Whether the acute pancreatitis mentioned by Guin (1976) should be regarded as a specific complication of the operation, remains uncertain; but damage to the pancreas may result from rough handling of the spatula used to keep the duodenum and the head of the pancreas out of the way. Sago et al. (1979) observed a few instances of severe pancreatitis after extensive suprarenal dissections. Lindsey and Glenn (1976) observed thrombosis of the renal vein in one patient. Another patient died as a result of intestinal infarction. The authors mention no cause of this complication, but ligation of the inferior mesenteric artery is undoubtedly a plausible cause.

VII.4.3 *Ejaculation disorders*

Ejaculation disorders are a common complications of retroperitoneal lymph node dissection; erection and orgasm are normal in these cases. The literature presents few publications on this subject. Yet it is certain that most patients have ejaculation disorders after a properly performed bilateral retroperitoneal lymph node dissection (Staubitz et al. 1974). Walsh et al. (1971) reported an incidence of 75%.

It is likewise certain that this complication is less frequent after unilateral lymph node dissections. Skinner (1976b) observed it in only 45% of his patients. On the other hand, Kedia et al. (1977) reported that 49 of the 52 patients were unable to ejaculate after a thoraco-abdominal lymph node dissection. In fact these authors go so far as to maintain that a dissection has not been properly performed when normal ejaculation is still possible afterwards.

The cause of the ejaculation disorders is the resection of the sympathetic trunk on either side of the vertebral column. It is generally assumed that, because the bladder neck does not close properly during ejaculation, semen enters the bladder: so-called retrograde ejaculation. Kom et al. (1971) and Kedia et al. (1977), however, were unable to demonstrate retrograde ejaculation; they ascribed non-ejaculation more to the absence of peristalsis in the ductus deferens and the inability of the seminal vesicles to contract.

Some authors maintain that these disorders are often transient (Leiter and Brendler 1967; Johnson 1976), but others are more pessimistic in this respect, believing that recovery is possible only via regeneration of nerve fibres, and in only a few patients (Kom et al. 1971; Kedia et al. 1977). Inability to ejaculate can be a serious problem in some cases, and in these cases it is in

fact the principal complication of retroperitoneal lymph node dissection. It has been found possible, however, to influence the contractility of the ductus deferens, seminal vesicles and bladder neck by medication, thus restoring normal ejaculation (Nijman et al. 1981).

Patients who require retroperitoneal lymph node dissection can be more or less assured of offspring by freezing of sperm. Unfortunately, however, precisely sperm from patients with a testicular tumour proves to be sub-normally fertile (Bracken and Smith 1980). Exhaustive research in this context is now in progress (Nijman et al. 1981).

In view of these facts, it is evident that the possibility of ejaculation disorders should always be discussed with the patient and his partner before a lymph node dissection is performed.

THE GRONINGEN PATIENTS

CHAPTER VIII

GENERAL DATA ON THE GRONINGEN PATIENTS

VIII.1 Number of patients

The data on which this study is based originate from the Division of Surgical Oncology, University Hospital, Groningen, where 147 patients with a non-seminomatous germ cell tumour of the testis were treated during the period 1963 through 1977. The majority had previously been treated by orchiectomy performed elsewhere.

All patients were submitted to an exhaustive study, including intravenous urography and in most cases also lymphography and tomography of the lungs. When the lymphogram was abnormal, a supraclavicular lymph node biopsy was performed. When the findings thus obtained showed that tumour growth was limited to subdiaphragmatic levels (stages I and II), a laparotomy was performed with the objective of performing retroperitoneal lymph node dissection. Of the 147 patients, 103 (70%) fulfilled the above criterion for laparotomy. The events in these 103 cases will be discussed. All histological primary tumour specimens and resected metastases in these 103 cases were revised by Dr. R. Eibergen (at the time pathologist at the Pathological Anatomical Laboratory, University Hospital, Groningen). Dr. J. M. H. Blom (radiologist, Military Hospital "Dr. A. Mathijsen", Utrecht) revised all the available lymphograms without receiving information on the case histories of these patients.

The minimum follow-up in this series was 3 years. The patients are given regular follow-up examinations up to 10 years after operation; these follow-ups are made every six weeks during the first year, every three months during the second, every four months during the third, and every six months during the fourth and the fifth year. Annual follow-ups are made during

the last five years. The examinations are made in an out-patient setting and include a plain chest X-ray and determination of the tumour markers HCG and AFP.

VIII.2 *Age distribution, orchiopexy, inguinal hernia operation, familial occurrence*

Of the 103 patients, 88 were referred to our department after an orchiectomy had been performed elsewhere. The remaining 15 patients underwent this operation in our department. The 103 patients averaged 31 years of age (range: 17 - 62). The age distribution in the entire group of patients is presented in fig. VIII.1.

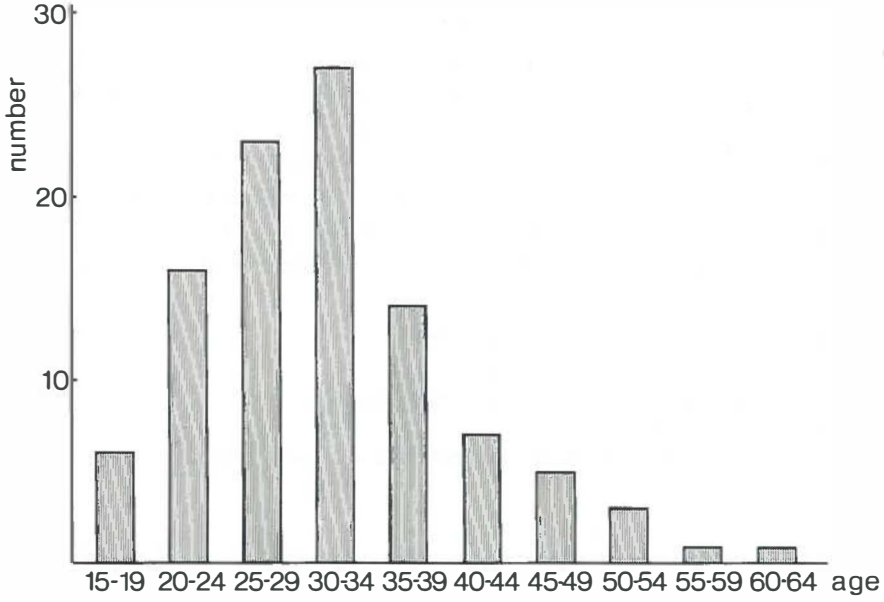


Fig. VIII.1 Age distribution of the 103 patients with a non-seminomatous tumour of the testis.

The primary tumour was localized in the right testicle in 57 (55%), and in the left in 46 (45%). Five patients (5%) had previously been treated for an undescended testicle by orchiopexy (bilateral operation in three). In all these cases the malignant tumour developed in the testicle fixed in the scrotum. Seven patients (7%) had a history of an inguinal hernia operation or were found to suffer from inguinal hernia at the orchiopexy. In five of these,

the inguinal hernia was localized on the same side as the tumour; in the remaining two the hernia was on the contralateral side. Two of the five patients previously treated by orchiopexy, had an inguinal hernia as well. One of the patients was found to have a brother who also had a non-seminomatous testicular tumour. This rare case has been described elsewhere as case report (Wobbes et al. 1981a). Two of the patients developed a malignant tumour in the contralateral testicle in the course of the follow-up period. In both cases a pure seminoma was diagnosed 18 and 36 months, respectively, after development of the non-seminomatous testicular tumour. These patients, too, have been previously described elsewhere (Hoekstra et al. 1981).

VIII.3 Histology of the primary tumour

Our department uses the histological classification of malignant testicular tumours proposed by Dixon and Moore (1953). Table VIII.1 presents a survey of this classification without group I (seminoma). As already pointed out in chapter V, this classification is based largely on the clinical behaviour of the neoplasm. Moreover, it is the classification most widely used along with that of Friedman and Moore (1946). The use of the Dixon and Moore (1953) classification facilitates comparison with other series of patients.

Embryonal carcinoma with or without seminoma (II)	35 (34%)
Teratoma with or without seminoma (III)	13 (13%)
Teratoma with embryonal carcinoma and/or choriocarcinoma with or without seminoma (IV)	51 (50%)
Choriocarcinoma with or without embryonal carcinoma and/or seminoma (V)	4 (4%)
	103

Table VIII.1: Classification of the 103 patients with a non-seminomatous germcell tumour of the testis on the basis of the histology of the primary tumour (classification according to Dixon and Moore (1953)).

Table VIII.1 also presents a survey of the histology of the primary tumour in our 103 patients. Two of these showed a purely infantile embryonal carcinoma which, as previously pointed out, cannot be readily fitted into this classification. In view of the clinical behaviour of this tumour, however, it can be included in the embryonal carcinoma group (II) without too much difficulty. Two other patients showed teratoma and seminoma with an admixture of infantile embryonal carcinoma (III). The pure form of chorio-

carcinoma was not found in this series, but in group V the choriocarcinoma component was invariably the largest component of the primary tumour. Group IV included 11 patients with some slight admixture of choriocarcinoma. This means that a total of 15 patients (15% of the 103) had choriocarcinoma components in the primary tumour.

VIII.4 Staging of patients after laparotomy

Laparotomy was performed when intravenous urography, pedal lymphography, a chest X-ray and (in some cases) supraclavicular lymph node biopsy had established that the tumour was confined to levels caudal to the diaphragm. In three cases a suspicion of inguinal lymph node metastases prompted an inguinal node biopsy, followed by inguinal node dissection.
Retroperitoneal lymph node dissection was performed in a total of 87 patients: transabdominal bilateral procedure in 86, and thoraco-abdominal operation in one patient. The technique of the two procedures has already been described in chapter VII.
Histological examination failed to reveal metastases in the retroperitoneal lymph nodes in 54 patients, who were therefore classified in stage I. Retroperitoneal node metastases were present but removable at primary laparotomy in 27 patients; in four patients this was impossible, but dissection was feasible after three courses of actinomycin-D (1 mg/day during 5 days every six weeks). This means that 31 patients had retroperitoneal lymph node metastases which could be dissected, with or without preceding chemotherapy. Finally, inguinal lymph node metastases were found in two patients with a history of orchiopexy. In both, retroperitoneal as well as inguinal lymph node dissection was performed. Para-iliac metastases existed in one of these patients. In another patient submitted to inguinal lymph node dissection, no inguinal node metastases were found.
In 14 patients the retroperitoneal tumour proved to be so extensive as to preclude lymph node dissection. Three patients showed suprahilar metastases as well.
A solitary metastasis was found in the liver in two patients. We refrained from retroperitoneal lymph node dissection in both cases because palpation revealed no retroperitoneal metastases and because, in view of the focus in the liver, both patients had to be classified in stage III.
As already mentioned in chapter V, we used the staging system of Skinner and Scardino (1980), as shown in table VIII.2. Patients with inguinal lymph node metastases do not fit into this system. Since we are dealing here with

loco-regional metastases, they are best classified in stage II; and the extent of metastatic growth in these two patients justifies their inclusion in stage IIB (listed in brackets in table VIII.2).

Stage I	(tumour confined to the scrotum)	54	
Stage IIA	(fewer than 6 nodes, $<$ 2 cm in diameter)	13	
Stage IIB	(6 or more nodes $\geq$ 2 cm in diameter/extracaps. spread)	18	(+2)
Stage IIC	("bulky disease")	14	
Stage III	(metastases above diaphragm or visceral metastases)	2	
		103	

Table VIII.2: Staging of the 103 patients with a non-seminomatous germ cell tumour of the testis after laparotomy or retroperitoneal lymph node dissection (staging system according to Skinner and Scardino (1980) (table V.3)).

VIII.5 Distribution of retroperitoneal metastases

Histological examination disclosed lymph node metastases in 32 of the 87 patients treated by retroperitoneal lymph node dissection. Metastases were found at the lumbar level in 31 patients (97%). In 15 (47%) they were confined to the ipsilateral side, nine patients (28%) had contralateral as well as ipsilateral lumbar metastases, and one patient had contralateral lumbar metastases only.

At the iliac level metastases were found in only one patient, without spread in cranial direction. This patient, however, had inguinal node metastases as well. The remaining four patients with iliac lymph node metastases had metastases at the lumbar level as well. In one, the iliac node metastasis was found on the contralateral side. In two patients finally the metastases were found between the aorta and the inferior vena cava.

Cross-over was found in 7 of the 19 patients with a right-sided tumour (37%). In one of these, the tumour had metastasized merely to the contralateral side, but another showed metastases also in the contralateral iliac region. Cross-over was found in 4 of the 13 patients with a left-sided tumour (31%), none of whom showed merely metastatic spread to the contralateral side. Contralateral lymph node metastases, therefore, were found in a total of 11 of the 32 patients (34%).

A solitary metastasis was found in 8 of the 19 patients (42%) with a right-sided tumour. In all patients except one it was confined to a lumbar level. Of 13 patients with a left-sided primary tumour, 3 (23%) showed a solitary metastasis at a lumbar level.

VIII.6 Correlation of the histology of the primary tumour with the pathological stage

The distribution of histological types of the primary tumour over the various pathological stages is shown in table VIII.3, in which patients with inguinal node metastases are listed separately.

	stage I	IIA	IIB	in-guinal nodes	IIC	III
Embryonal carcinoma with or without seminoma (II)	10	9	10	2	4	—
Teratoma with or without seminoma (III)	8	2	—	—	2	1
Teratoma with embryonal carcinoma and/or choriocarcinoma with or without seminoma (IV)	33	1	8	—	8	1
Choriocarcinoma with or without embryonal carcinoma and/or seminoma (V)	3	1	—	—	—	—
	54	13	18	2	14	2

Table VIII.3: Distribution of the histological types of the primary tumour over the pathological stages.

Choriocarcinoma components were found in 7 (21%) of the 33 stage I patients with a tumour classified in group IV according to Dixon and Moore (1953), and in four (50%) of the eight stage IIB patients with a group IV tumour. The two patients with a purely infantile embryonal carcinoma were in stages IIA and IIC, respectively. The two patients with admixture of these components were in stages I and IIC, respectively.

VIII.7 Histology of the metastases

The histology of the metastases was identical to that of the primary tumour in 17 of the 33 patients in whom radically removable lymph node metastases were found. In one patient treated with actinomycin-D prior to dissection, the lymph nodes proved to contain only necrotic tumour tissue. In the remaining 15 patients, however, either different or fewer histological components were found in the metastases. In some cases, moreover, the ratio between the various histological components was found to have changed. In two cases the lymph node metastases contained only seminoma tissue, although the primary tumour was an embryonal carcinoma in one, and a pure teratoma in the other.

In a number of the 14 patients in whom retroperitoneal lymph node dissection was found to be impossible, information on the histology of the metastases was nevertheless obtained via biopsy or partial dissection. Since the metastatic tissue could not be removed in toto it was not justifiable in these cases to compare the histology of the metastases with that of the primary tumour.

VIII.8 Discussion

The observation that malignant testicular tumours are slightly more frequently found on the right than on the left side, is corroborated by other authors (Collins and Pugh 1964; Johnson 1976). Whether this correlates with an increased incidence of undescended testis and congenital inguinal hernia remains uncertain. It seems plausible, however, since the risk of development of a malignant testicular tumour is increased in patients with an undescended testis, and possibly also in those with congenital inguinal hernia ascribed to dysgenesis of the genital system.

The series of 103 patients included five instances of malignant degeneration in a previously undescended testis; the anomaly was bilateral in three of these cases. In all cases, orchiopexy had been performed at ages 12-22 years. In a Groningen series of 287 patients, including 102 with a seminoma, 5.6% had a history of undescended testis. The mean age at orchiopexy in this group was 14 years. In none of the patients had orchiopexy been performed before the 6th year of life (Wobbes et al. 1980b).

It is a conspicuous fact that a malignant testicular tumour was never found when orchiopexy had been performed before the 6th year of life (Martin and Menck 1975; Gehring et al. 1974). It is therefore not surprising that early orchiopexy has been more and more urged in recent years, in part also because the fertility of the testicle involved is believed to be favourably influenced by it. Mengel et al. (1974) and Hadziselimowic et al. (1975) found that normal fertility can be expected when the testis is restored to the scrotum before the second year of life. Another unmistakable trend favours removal of the undescended testis after puberty, rather than fixation in the scrotum. In view of our data, we too regard this as the treatment of choice.

Congenital inguinal hernia was found in the history in seven cases (7%). This is a relatively large percentage in view of the fact that the normal incidence is 0.8 - 4.4% (Mustard et al. 1969). The incidence of congenital inguinal hernia in the above-mentioned series of 287 Groningen patients was 4.9% (Wobbes et al. 1980b).

Lymph node dissection was performed in three of the five patients who had been treated by orchiopexy in the past. Metastases were found in the inguinal lymph nodes in two of them, and in one of them there were para-iliac metastases as well. In none of the five patients who underwent an inguinal hernia operation on the same side as the malignant testicular tumour was lymph node dissection performed. Yet metastasis to the inguinal lymph nodes can be expected after an inguinal hernia operation on theoretical grounds. The findings obtained in one of the 287 Groningen patients (Wobbes et al. 1980b) confirm the theoretical expectation. In all patients with an inguinal operation in the history, therefore, inguinal lymph node dissection should receive due consideration.

As regards primary tumour histology (table VIII.3) we find that the teratocarcinoma group (IV) occurs more frequently than the embryonal carcinoma group (II). Comparing these data with those in table V.2, we find that teratocarcinoma is overrepresented in our series. Perhaps the explanation is that the series is smaller than the one on which the figures presented in table V.2 are based. This difference in distribution may exert a favourable influence on the therapeutic results in the Groningen series, for the prognosis of teratocarcinoma is generally regarded as better than that of embryonal carcinoma (see table VI.4).
Table VIII.3 indicates that teratocarcinoma is more frequent in stage I (33/54, 61%) than in the joint stages II (with inguinal lymph node metastases) (17/47, 36%). Embryonal carcinoma, on the other hand, is more frequent in stage II (25/47, 53%) than in stage I (10/54, 18.5%). This might indicate that embryonal carcinoma is more likely to metastasize than teratocarcinoma - a finding corroborated by other investigators (Van der Werf-Messing 1980).

A difference in histology between metastases and primary tumour is not uncommon (Nochomowitz et al. 1977). A possible explanation is that the primary tumour was insufficiently examined so that small areas with certain components were overlooked. An interesting question is whether patients with seminoma only in the metastases should receive other treatment than those with pure seminoma in the primary tumour as well as in the retroperitoneal metastases. Should the mediastinum and supraclavicular areas be irradiated as well, and should adjuvant therapy follow? In our opinion this decision depends in part on the presence or absence of tumour markers before and after node dissection.

The figures on the distribution of the retroperitoneal metastases roughly correspond with those reported by other authors (Fein and Taber 1969; Hultén et al. 1973; Storm et al. 1977). In all patients, metastases were in fact found either only at a lumbar level or at a lumbar and an iliac level. The solitary para-iliac lymph node metastasis demonstrated in the patient with an inguinal node metastasis should be regarded as a secondary lymph node site. Not a single instance was therefore seen of solitary metastasis to para-iliac lymph nodes, as reported by Ray et al. (1974).

In our series the right-to-left and left-to-right cross-over percentages were 37 and 31, respectively. This would seem to indicate that right-to-left cross-over is as frequent as left-to-right cross-over. This contradicts the findings reported by Hultén et al. (1973) and Storm et al. (1977) but corresponds with those of Ray et al. (1974) (see section III.4). In any case this finding is an argument in favour of bilateral retroperitoneal lymph node dissection.

A striking finding in one patient was the presence of para-iliac lymph node metastases on the contralateral side. An implication of this finding may be that retroperitoneal lymph node dissection for metastases on the contralateral side should always be extended to the para-iliac nodes. With the thoraco-abdominal approach, however, access to this area is far more difficult. This, in fact, can be used as an argument against this technique.

Only three patients (3%) showed metastases cranial to the renal vascular pedicle; in these cases, however, extensive metastasis was found also caudal to the renal hilus. Solitary metastases cranial to the hilus were not found, nor did metastases of this type develop in any case in the course of the follow-up.

A remarkable finding was that of a solitary liver metastasis in two patients in whom no retroperitoneal lymph node metastases were identified. The literature comprises no reports on a similar situation. A liver scan is not part of preoperative routine because primary spread of malignant testicular tumours to the liver is exceedingly unusual. Moreover, even a liver scan has its limitations in the diagnosis of metastases. If no laparotomy had been performed, then these metastases would not have been detected until much later. These two patients support the postulate that laparotomy is the method of choice for adequate staging of non-seminomatous testicular tumours.

CHAPTER IX

METHODS OF TREATMENT AND RESULTS

In the course of the years covered by this study , the treatment of patients has not remained entirely unchanged. However the retroperitoneal lymph node dissection has always remained as the basis for treatment. It is therefore possible to distinguish several large groups of patients given uniform treatment.
The therapeutic results obtained in the various stages will be discussed in succession.

IX.1 Stage I

As already mentioned in chapter VIII, 54 of the 103 patients had no demonstrable metastases in the retroperitoneal lymph nodes. In all except two of these patients, retroperitoneal lymph node dissection was the only treatment given. One patient received 2500 rad (25 Gy) irradiation in 3 weeks after the operation (orthovoltage) on lumbar and para-iliac areas. The other patient received 1200 rad (12 Gy) in 2 weeks (orthovoltage) on a lumbar area. The data on the patients provided no argument in favour of this radiotherapy.
During the follow-up period, which ranged from 5 to 16 months, lung metastases developed in 5 of the 54 patients (9%). One develop a para-iliac contralateral lymph node metastasis which became manifest after 16 months. The clinical data on these patients are outlined in table IX.1.
Two of these six patients died. Patient no. 2 died of the results of metastatic spread; patient no. 4, who was 62 years old, died an acute death at home, probably due to myocardial infarction. In the latter patient the lung metastases had shown complete regression after three courses of actinomycin-D.

Patient	Histology primary tumour	site of recurrence	interval	treatment	survival
1	teratocarcinoma	lung	12 months	act-D/Vbl/RT	alive
2	teratocarcinoma	lung	10 „	act-D/Vbl	21 months
3	teratocarcinoma	lung	16 „	act-D/RT/surg.	alive
4	embryonalcarcinoma	lung + loc.rec.	5 „	act-D/surg.	9 months
5	embryonalcarcinoma	lung	8 „	act-D/Vcr/Vbl/Bl/ Cispl/RT/surg.	alive
6	teratocarcinoma	retroperi-toneum	16 „	Cispl/Vbl/Bl/surg.	alive

Table IX.1: Non-seminomatous tumours of the testis stage I. Survey of some clinical data on 6 patients who relapsed after orchiectomy and retroperitoneal lymph node dissection. (See Table IX.4 for abbreviations used).

The actinomycin-D routinely given in our department is programmed as follows. During five days in hospital, the patient receives 1 mg actinomycin-D daily by continuous intravenous drip over 6-8 hours. This course is repeated every six weeks over a two-year period, unless the metastases show no favourable response.

The remaining four patients (nos. 1, 3, 5 and 6) showed complete remission of the metastases in response to treatment, and had no demonstrable tumour growth after a minimum follow-up period of three years. Patient no. 5 (with negative tumour markers) received chemotherapy followed by thoracotomy. Mature teratoma tissue was found. Patient no. 6 was the only patient in stage I to develop retroperitoneal metastases at the contralateral iliac level. He was given four induction courses with cis-platinum, vinblastine and bleomycin (Einhorn and Williams 1978), whereupon a well-encapsulated tumour was extirpated; the sigmoid and the left ureter had to be sacrificed in this operation. Histological examination of the resected specimen showed that the tumour was largely necrotic but also still contained mature teratoma and vital embryonal carcinoma. After the operation this patient received maintenance therapy with cis-platinum, vinblastine and bleomycin as described by Stoter et al. (1979). He is at present tumour-free.

The 3-year survival of the 54 patients in stage I was 96% (fig. IX.1). It was found that 89% of the patients remained free of demonstrable tumour growth at least three years after primary treatment (recurrence-free survival).

IX.2 Stages IIA and IIB

The treatment of the 31 patients in stages IIA and IIB has been subject to some variation in the course of the years. This is shown in table IX.2. Treatment consisted solely of retroperitoneal lymph node dissection during the period 1963-1968 (four patients). During the period 1968-1974, adjuvant actinomycin-D as well as radiotherapy was added. The actinomycin-D was administered as outlined in section IX.1. Irradiation was of the orthovoltage type before 1970, but megavoltage therapy (^{60}Co) has since been used. The dosage was 3000 rad (30 Gy) in 3 weeks on para-aortic and para-iliac areas, followed by a boost of 2000 rad (20 Gy) in 2-3 weeks on the site from which the tumour had been removed. Moreover, mediastinum and a bilateral supraclavicular area were exposed to 3000 rad (30 Gy) in 3 weeks. The total duration of radiotherapy was 6 weeks or longer.

Three patients received only radiotherapy after retroperitoneal lymph node dissection. In two, this option was taken because the retroperitoneal lymph nodes contained only seminoma tissue. In the third case the psychological stress of two years of actinomycin-D medication seemed too much. The radiotherapy dosage was 3000 rad (30 Gy) on lumbar and iliac areas in 3 weeks, and 3000 rad (30 Gy) on mediastinum and supraclavicular area in 3 weeks.

From 1975 to 1977, the only therapy given in addition to retroperitoneal lymph node dissection was adjuvant actinomycin-D.

	number of patients	3-year survival	5-year survival
Retroperitoneal lymph node dissection alone (1963-1968)	4	2/4 (50%)	2/4 (50%)
Retroperitoneal lymph node dissection + radiotherapy	3	1/3 (33%)	1/3 (33%)
Retroperitoneal lymph node dissection + radiotherapy + chemotherapy (1968-1974)	10	8/10 (80%)	8/10 (80%)
Retroperitoneal lymph node dissection + chemotherapy (1975-1977)	14	13/15 (93%)	—
	31	24/31 (77%)	

Table IX.2: Non-seminomatous tumours of the testis stage IIA and IIB. Survey of 3-year and 5-year survival rates in four groups of patients treated by retroperitoneal lymph node dissection alone or in combination with various forms of adjuvant therapy.

Table IX.2 presents a survey of the results of the various types of therapy. The 3-year survival of the entire group of patients in stages IIA and IIB was 77%. The 3-year survival without evidence of metastases during a follow-up of at least 3 years was 74% (23/31). When stage II patients are subdivided into those in substages IIA and IIB, no difference in survival is found between the two subgroups. The 3-year survival of the 13 patients in stage IIA was 77% (10/13), versus 78% (14/18) in stage IIB.
Eight patients (26%) developed metastases in the course of the follow-up over 5-18 months. Data on these patients are presented in table IX.3. Six patients developed only lung metastases, one had pulmonary and mediastinal metastases and another had only supraclavicular metastases. Three of the eight patients who developed metastases during the follow-up were in stage IIA (23%), five were in stage IIB (28%).

Patient	Histology primary tumour	adjuvant treatment	site of recurrence	interval	treatment	survival
7	embryonal carcinoma	none	lung + med.	12 months	MTX/Vbl	33 months
8	embryonal carcinoma	none	lung	12 „	none	24 months
9	embryonal carcinoma	RT	lung	9 „	surg.	12 months
10	terato-carcinoma	RT	supraclav.	14 „	act-D/Vbl/Bl	36 months
11	terato-carcinoma	RT/act-D	lung	5 „	Vbl/Bl	16 months
12	embryonal carcinoma	RT/act-D	lung	7 „	Vbl/Bl/surg.	alive (5-year)
13	chorio/terato-carcinoma	RT/act-D	lung	5 „	Vbl/Bl	15 months
14	terato-carcinoma	act-D	lung	18 „	Vbl/Bl	34 months

Table IX.3: Non-seminomatous tumours of the testis stages IIA and IIB. Survey of some data on patients who relapsed after retroperitoneal lymph node dissection with or without subsequent adjuvant therapy.

Four patients developed lung metastases during the adjuvant treatment with actinomycin-D (nos. 11, 12, 13 and 14), whereupon this agent was replaced by a combination of vinblastine and bleomycin (every week on dag 1 10 mg

vinblastine intravenously and on day 3 15 mg bleomycin intramuscularly). In patient no. 10, actinomycin-D was started when the supraclavicular lymph node metastasis was detected. No regression was achieved.
Three of the five patients treated with vinblastine and bleomycin showed radiological evidence of partial regression of the lung metastases. In one (no. 12) the lung metastases could be extirpated; this patient has a recurrence-free survival of 5 years. The other two showed an increase in the size of the metastases after some time. The remaining two showed no response whatever to treatment with vinblastine and bleomycin.

Inguinal lymph node metastases were found in two patients with an inguinal operation in the history. One had para-iliac lymph node metastases as well. Both were given the usual actinomycin-D after retroperitoneal and inguinal lymph node dissection. These two also showed 3-year recurrence-free survival.
This gives us a total of 16 patients with loco-regional lymph node metastases radically removable by dissection, whose only additional treatment was adjuvant actinomycin-D. Only one developed pulmonary metastases. In four of these 16 cases retroperitoneal lymph node dissection was not feasible until after three actinomycin-D courses. In one of these, the metastases proved to have become completely necrotic; partial regression was achieved in three. The 3-year recurrence-free survival in this group of 16 patients was 94%.
Of the 10 patients who received not only radiotherapy but also adjuvant actinomycin-D over a two-year period, three developed lung metastases. In one of these, complete remission was achieved by a combination of chemotherapy, radiotherapy and surgery. In the other two (one of whom had a primary tumour of group V in the Dixon and Moore (1953) classification), all therapeutic efforts failed. The 3-year survival in this group of patients was 80% (recurrence-free survival 70%).

The 3-year survival for the total group of 33 (31 + 2) patients with loco-regional lesions removable by dissection was 79% (26/33) (fig. IX.1). The 3-year recurrence-free survival in this group was 76% (25/33).
Of the 26 (16 + 10) patients with loco-regional lesions given adjuvant actinomycin-D, four (15%) developed lung metastases. Of the seven patients given no adjuvant therapy or only radiotherapy, three (43%) developed lung metastases, and one developed supraclavicular metastases.

IX.3 Stage IIC

The initial laparotomy revealed extensive retroperitoneal lymph node metastases in 14 patients. Three showed metastases cranial to the renal vascular pedicle as well. Extirpation of the retroperitoneal metastases was impossible in all these cases. In a few, a biopsy was performed or tumour parts were resected for histological examination. Table IX.4 presents a survey of the clinical data on these 14 patients.

The total number of laparotomies performed in this group was 25. In 11 patients, actinomycin-D was started after the initial laparotomy. In five (nos. 19, 21, 23, 24 and 25) this treatment was combined with radiotherapy; in one of these (no. 24) the retroperitoneal metastases were extirpated. As a rule, a second laparotomy was performed after three actinomycin-D courses for evaluation of the effect. In patient no. 18 the tumour could be removed at the second laparotomy. Of the five patients given actinomycin-D combined with radiotherapy, three achieved partial and one complete remission; one showed no effect. Two patients with partial remission were subsequently treated with cis-platinum, vinblastine and bleomycin (nos. 23 and 25), while the third (no. 24) received cis-platinum, adriamycin and cyclophosphamide. Two of them ultimately died from pulmonary metastases, and the third died from sepsis as a therapeutic complication.

Three patients (nos. 20, 22 and 26) received vinblastine and bleomycin in accordance with the above-mentioned programme after two or three actinomycin-D courses. These three achieved only partial remission and ultimately died from lung metastases. In two patients (nos. 27 and 28), three actinomycin-D courses were followed by treatment with cis-platinum, vinblastine and bleomycin. In one, the primary treatment with actinomycin-D had been partly effective; in the other, the second laparotomy revealed that liver metastases had developed. The first patient (no. 27) attained complete remission but died from myocardial infarction after 12 months. The second (no. 28) died as a result of cytostatic medication.

The remaining three patients in the earliest group (nos. 15, 16 and 17) always received radiotherapy. In no. 15, the retroperitoneal tumour mass could be removed afterwards; this patient has 16 years of recurrence-free survival. In no. 17 the tumour could only partly be removed; tumour growth continued despite methotrexate and finally led to fatal anuria. Patient no. 16 developed lung metastases after retroperitoneal irradiation.

Of the 14 patients in stage IIC, 8 ultimately developed organ metastases (lung metastases in six and liver metastases in two). Only three patients

patient	histology primary tumour	primary treatment	effect	further treatment	effect	further treatment	survival
15	teratocarcinoma	RT/surg	CR				alive (16 year)
16	teratocarcinoma	RT	none				9 months (lung metast.)
17	teratocarcinoma	RT/MTX/surg	none				7 months (retroper.rec.)
18	teratocarcinoma	Act-D (16×)	PR	surg.			alive (11 year)
19	infant.embryonal carcinoma	RT/Act-D (3×)	none				8 months (liver metast.)
20	embryonalcarcinoma	Act-D (2×)	none	Vbl/Bl	PR		9 months (lung metast.)
21	teratoma	RT/Act-D (16×)	CR				alive (17 year)
22	embryonalcarcinoma	Act-D (3×)	none	Vbl/Bl	PR		10 months (lung metast.)
23	teratoma	Act-D (5×)	none	RT/Act-D (9×)	PR	Cispl/Vbl/Bl	21 year (sepsis)
24	teratocarcinoma	Act-D (3×)	none	RT/surg/Act-D (5×)	PR	Cispl/Adr/Cfm	30 months (lung metast.)
25	teratocarcinoma	Act-D (3×)	none	RT/Act-D (5×)	PR	Cispl/Vbl/Bl	38 months (lung metast.)
26	teratocarcinoma	Act-D (3×)	none	Vbl/Bl/RT	PR		15 months (lung metast.)
27	embryonalcarcinoma	Act-D (3×)	PR	Cispl/Vbl/Bl	CR		24 months (myocard inf.)
28	teratocarcinoma	Act-D (3×)	none	Cispl/Vbl/Bl			8 months (sepsis, liver metast.)

Table IX.4: Non-seminomatous tumours of the testis stage IIC. Survey of some clinical data on 14 patients whose retroperitoneal metastases could not be removed.

(Abbreviations: Act-D = actinomycine-D, Vbl = vinblastine, Bl = bleomycin, Cispl = cisplatinum, Adr = adriamycin, Cfm = cyclophosphamide, MTX = methotrexate, surg = surgery, RT = radiotherapy, PR = partial remission, CR = complete remission).

(21%) attained prolonged recurrence-free survival (fig. IX.1). Patient no. 23 with a teratoma died 21 years after orchiectomy from sepsis resulting from chemotherapy; throughout these years he had never been tumour-free.

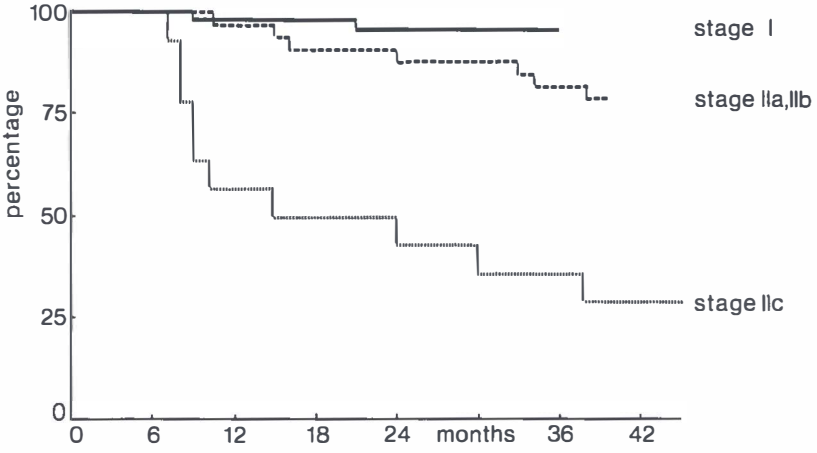


Fig. IX.1 Survival rate of the patients by stage.

IX.4 Stage III

Two patients who seemed to be in stage II prior to laparotomy, had liver metastases. Palpation revealed no retroperitoneal lymph node metastases. In one, the tumour was irradiated (7500 rad (75 Gy) in 6 weeks), leading to 10-year recurrence-free survival. In the other, the liver metastasis was excised, followed by two years of actinomycin-D adjuvant therapy. This patient is still alive without demonstrable tumour growth after 7 years.

IX.5 Distribution of organ metastases according to histology of the primary tumour

The distribution of organ metastases over the various histological types is shown in table IX.5.

Patients in stages IIA and IIB and those with inguinal and para-iliac lymph node metastases have been lumped together, because separate consideration of these substages would have given numbers too small to warrant conclusions.

Stage I shows a predominance of organ metastases in embryonal carcinoma (20%) versus teratocarcinoma (9%). In the other stages possible differences are less pronounced.

Stage I n = 54	number of patients	organmetastases
embryonal carcinoma	10	2 (20%)
teratoma	8	—
teratocarcinoma	33	3 (9%)
choriocarcinoma	3	—
	54	5 (9%)

Stages IIA and IIB (+ inguinal lymph node metast.) n = 33	number of patients	organmetastases
embryonalcarcinoma	21	4 (19%)
teratoma	2	—
teratocarcinoma	9	2 (22%)
choriocarcinoma	1	1
	33	7 (21%)

Stage IIC n = 14	number of patients	organmetastases
embryonalcarcinoma	4	3 (75%)
teratoma	2	—
teratocarcinoma	8	5 (62.5%)
choriocarcinoma	0	—
	14	8 (57%)

Stage III n = 2	number of patients	organmetastases
embryonalcarcinoma	—	
teratoma	1	
teratocarcinoma	1	
choriocarcinoma	—	
	2	

Table IX.5: Distribution of organ metastases according to stage and histology of the primary tumour.

Of the four patients with a tumour that largely consisted of choriocarcinoma, only one developed lung metastases in stage IIB. Of the three stage I patients whose tumour contained choriocarcinoma components (group V in the Dixon and Moore (1953) classification), none developed lung metastases. One stage IIC patient with an infantile embryonal carcinoma ultimately died from the consequences of liver metastases.

IX.6 Discussion

The therapeutic results in the patients in stage I correspond with those reported by other authors who confined themselves to retroperitoneal lymph node dissection (table VI.1). Comparison with the results reported by authors who added radiotherapy to node dissection leads to the conclusion that radiotherapy contributes nothing to the therapeutic results. The principal objection to retroperitoneal irradiation in stage I is that this is not the site at which the tumour is likely to recur after primary therapy. Gilbert et al. (1976) studied the localization of metastases in patients who ultimately died from a non-seminomatous testicular tumour. Of the 35 stage I patients, eight died and retroperitoneal lymph node metastases were found in only one. Only in this case might radiotherapy have been useful.

In our opinion the results also indicate that the patients in stage I require no adjuvant chemotherapy after node dissection either, as Skinner (1976) advocated. The rationale of adjuvant chemotherapy is to destroy micrometastases which can develop to organ metastases. Five of the 54 patients in stage I (9%) ultimately developed lung metastases. Although cis-platinum was not yet available at the time, permanent remission was achieved in three cases. This would probably have been possible in all cases had combined chemotherapy (cis-platinum, vinblastine and bleomycin) been available (Donohue et al. 1979). We believe that it is sufficient to perform regular tumour marker assays in serum, for an abnormality in tumour markers is usually the first manifestation of metastatic growth, as the case history of patient no. 6 demonstrates. This case history also demonstrates that the above-mentioned combination of chemotherapeutic agents can achieve a complete remission.

As already mentioned in chapter VI, the question even arises whether orchiectomy should indeed be followed by retroperitoneal lymph node dissection in patients in stage I with negative tumour markers. Is it not sufficient to perform a laparotomy with, if necessary, removal of a few lymph nodes for histological examination, as in Hodgkin's disease?

The therapeutic results obtained in stages IIA and IIB would seem to warrant three conclusions. Of seven patients given no or only radiotherapy after retroperitoneal lymph node dissection, three (43%) developed lung metastases. Of the 26 patients with loco-regional lesions given adjuvant actinomycin-D routinely, only four (15%) developed lung metastases. Although the numbers are small, they would seem to indicate first of all that

retroperitoneal lymph node dissection should be followed by adjuvant therapy in stage II. This therapy should aim at destruction of the micrometastases that can ultimately produce manifest organ metastases.
The second conclusion is that radiotherapy after retroperitoneal lymph node dissection has no positive effect on survival of patients in stages IIA and IIB (see table IX.2). This irradiation is to destroy tumour cells left in situ. Local recurrence was not observed in our series and we believe that tumour spill is minimal after careful node dissection. Any tumour cells nevertheless left in situ, will be unable to develop due to adjuvant chemotherapy. Moreover, as already mentioned in chapter VI, some authors have reported a diminished efficacy of chemotherapy in tumour recurrence in patients previously given radiotherapy (Stoter et al. 1979).
The third conclusion is that actinomycin-D as given in the manner outlined, is an effective adjuvant drug. It has been pointed out that little is known about the use of actinomycin-D as adjuvant chemotherapeutic agent. Table IX.6 presents a survey of the results reported by a number of authors who gave only actinomycin-D after retroperitoneal lymph node dissection.
In the patients treated by Merrin and Murphy (1974), the lung metastases could be removed by resection. The patients of Williams et al. (1980) were given cis-platinum, vinblastine and bleomycin after lung metastases developed. Few data are available on the series described by Edson (1979). None of the authors mentioned specified the staging system used, and we therefore have no information on the extent of retroperitoneal metastasis.

	lung metastases	3-year survival
Merrin and Murphy (1974)	3/9 (33%)	8/9 (89%)
Edson (1979)	unknown	15/20 (75%)
Williams et al. (1980)	15/31 (48%)	30/31 (97%)
Groningen series (1981)	1/16 (6%)	15/16 (94%)

Table IX.6: Non-seminomatous tumours of the testis stages IIA and IIB. Development of lung metastases after retroperitoneal lymph node dissection followed by adjuvant actinomycin-D as a single agent.

The publication of Williams et al. (1980) shows that, when lung metastases develop in spite of the administration of actinomycin-D, remission nevertheless can be achieved in a large number of cases by giving the combination of cis-platinum, vinblastine and bleomycin.
Why adjuvant actinomycin-D produced such favourable results in this series as compared with others, remains uncertain. Perhaps the mode of admini-

stration is of importance in this respect. We give the daily dose of actinomycin-D by continuous intravenous drip over a period of 6-8 hours. The mode of administration used by others authors is unknown.
Samuels et al. (1979b) reported favourable results obtained with adjuvant therapy by a combination of vinblastine and bleomycin. The various dosage schemes for these agents have been outlined in chapter VI. The authors achieved 5-year survival in 85% of 37 patients. Two died as a result of the therapy.
We can compare these results with our 88% 3-year survival in 26 patients given adjuvant actinomycin-D only. The comparison would seem to warrant the conclusion that results obtained with vinblastine/bleomycin and those with actinomycin-D alone are equivalent. Bleomycin, however, entails a grave risk of interstitial pneumonitis. On the other hand, the question arises whether adjuvant chemotherapy should really be given in all stage II cases. The results obtained with the combination of cis-platinum, vinblastine and bleomycin in stage II, after all, are very good (Einhorn and Donohue 1979; Stoter et al. 1979). Should we therefore give adjuvant chemotherapy only in stage IIB, and adopt an expectant attitude in stage IIA? In the Groningen series there was no difference in survival between those patients in stage IIA and those in stage IIB (77% and 78%, respectively). Nor was there a difference in incidence of lung metastases.
These similarities in results can be explained by the fact that the patients were treated with actinomycin-D, which prevented some of the micrometastases from developing. Theoretically, however, the number of lung metastases developed during the follow-up should be smaller in stage IIA than in stage IIB. It is therefore not surprising that some investigators decided to discontinue adjuvant chemotherapy in stage IIA (minimal disease) (Fraley et al. 1977; Vugrin et al. 1979).
Samuels et al. (1979b), on the other hand, adhered to adjuvant chemotherapy in all stage II cases but, in view of the side effects of cis-platinum (nephrotoxic and ototoxic effects), gave only a combination of vinblastine and bleomycin.
In our department the decision has been made - partly on the basis of personal experience and partly in view of reports in the literature - to discontinue adjuvant chemotherapy in stage IIA. However, the question remains which chemotherapeutic agent or combination of agents is to be given in stage IIB. Should a combination of cis-platinum (P), vinblastine (V) and bleomycin (B) be given, or should we adhere to actinomycin-D medi-

cation? Each of the former agents, after all, has its toxic side effects. Actinomycin-D also produces side effects, but recovery from these effects seems more complete. Not much is known about the long-term side effects of the PVB combination, but permanent damage to renal function and to hearing seems likely.
In order to find a definite answer to the question of the agent or combination of choice, a prospective randomized study should be designed with special focus on the side effects of the various agents. Of course the number of lung metastases will be larger in the actinomycin-D group. But even in these cases the PVB programme can ensure ultimate complete remission. The advantage lies in the fact that not all patients are exposed to the side effects of PVB when actinomycin-D is regarded as first choice agent.

Our experience with patients in stages I, IIA and IIB who developed lung metastases, is less favourable. Four of the 12 ultimately survived. The combination of vinblastine and bleomycin in the doses we used has proved to be insufficient to ensure complete remission. A partial remission was achieved in only three of the five patients in stages IIA and IIB, and in three patients in stage IIC.
Considering the therapeutic results obtained in patients with extensive retroperitoneal metastases, we are forced to conclude that actinomycin-D is not very effective when used to induce remission. Of the 11 patients in stage IIC primarily given only this cytostatic, two achieved partial remission (which is to say that at the second laparotomy the metastases had diminished in size). Of the four patients in stage IIB found primarily inoperable but submitted to retroperitoneal lymph node dissection after three actinomycin-D courses, one had metastases found to be completely necrotic on histological examination, while the three others showed partly necrotic metastases. One patient in stage I who developed lung metastases during the follow-up, showed complete remission of these metastases in response to actinomycin-D. A more prolonged follow-up on this patient was impossible because he died intercurrently.

Of the total of 16 patients with demonstrable tumour treated solely with actinomycin-D, five (31%) had a partial an two (12.5%) a complete remission. Partial remission is defined here as diminution of lymph node or lung metastases during or after therapy. An exact measure cannot be given in this retrospective study. The overall response rate to actinomycin-D alone was

44%; this is in excess of the 33% reported by Jacobs and Muggia (1979). The complete remission rate of 12.5% in our patients, however, is below the 18% reported by these authors. We must therefore conclude that actinomycin-D alone is of little value as remission-inducing agent.

Of the 14 patients in stage IIC four were treated with the PVB combination (Einhorn and Donohue 1979b); one was treated elsewhere with a combination of cis-platinum, adriamycin and cyclophosphamide. Two of these patients (nos. 22 and 28) died due to side effects during treatment. One of them had been previously irradiated. Two others (nos. 24 and 25), also previously treated by actinomycin-D and irradiation, ultimately died due to lung metastases. Only one patient previously given only actinomycin-D achieved complete remission. This patient, aged 43, died a year later as a result of myocardial infarction.

A review of the results obtained with these cytostatics reveals that in our patients they were not favourable. There are two possible explanations. The first is that little experience has been gained with the PVB programme during the period 1977-1978. The second is that, in this context too, it is evident that the therapeutic effect diminishes when the patient has previously received radiotherapy (Donohue et al. 1977; Stoter et al. 1979).

The 3-year survival was 36% (5/14) and the 5-year survival was 28.5% (4/14) in stage IIC. This is low in comparison with that in other groups of patients with extensive lesions who were treated by the PVB programme in combination with adjuvant surgery. Donohue et al. (1980) observed complete remission in 80% of the patients. Our subsequent experience with this mode of treatment is likewise favourable (Stoter et al. 1979). PVB therapy, therefore, has significantly improved the prognosis in patients with extensive retroperitoneal lymph node metastases of a non-seminomatous testicular tumour.

Considering the entire group of 47 patients in stage II, we find a 3-year survival of 66% (31/47). Two of these patients (in stage IIC) still showed demonstrable tumour growth after 3 years. The recurrence-free survival for the entire group was 62% (29/47). As already mentioned earlier in this chapter, teratocarcinomas seem to have a more favourable prognosis than embryonal carcinomas. The percentage of organ metastases developing in stage I with the various tumour types likewise indicates that teratocarcinomas are less malignant in biological behaviour than embryonal carcinomas. This difference is not clearly expressed in stage II, but the finding is not contradicted in this stage. The explanation may be that patients of this group

were treated with cytostatics, which interfered with the natural course. Another possible implication is that embryonal carcinomas are more sensitive to chemotherapy.

CHAPTER X

COMPLICATIONS OF THERAPY

X.1 Introduction

As already explained in chapter VII, various complications may develop during and after retroperitoneal lymph node dissection, some of which are fairly specific for this procedure, while others can occur after any intra-abdominal operation. The complications of the 120 laparotomies performed in the 103 patients of our series are listed in table X.1.
It is of importance to note that no mortality was recorded. Although ejaculation disorders are also among the complications of retroperitoneal lymph node dissection, they are not included in table X.1 but will be separately discussed. The complications are divided into "major complications" and "other complications". The former all developed in patients treated by retroperitoneal lymph node dissection.

X.2 "Major complications"

"Major complications" are defined as complications which are a threat to the patient's life or necessitate sacrifice of organs. A "major complication", for example, is damage to a ureter as inflicted in two patients (on the right ureter in both cases). In one patient the damaged ureter was repaired during the operation, but a retroperitoneal abscess developed in assciation with an ureteral fistula. Nephro-ureterectomy had to be performed two months later. The other patient developed hydronephrosis of the right kidney after a few months. Roentgenography revealed an obstruction in the distal ureter. Exploration showed that the continuity of the ureter was disturbed. Repair was impossible, and nephro-ureterectomy had to be performed. Both patients are still alive after a recurrence-free period of 14 years and 6 years, respectively.

"Major complications"	
damaged ureter (nephro-ureterectomy)	2
damaged spleen (splenectomy)	1
postoperative haemorrhage	2
coagulation disorders	1
distress syndrome	1
Other complications	
respiratory infection	4
thrombosis	1
wound haematoma	1
wound abscess	1
suture fistulae	1
cicatricial hernia	1
urinary infection	5
stenosis of meatus urinarius	1
contralateral hydrocele	10

Table X.1: Survey of the complications of 120 laparotomies in 103 patients. All "major complications" developed after retroperitoneal lymph node dissection.

In one case, the spleen was so damaged during retroperitoneal lymph node dissection that splenectomy was required. During an adjuvant actinomycin-D course this patient developed bacterial meningitis, but recovered.
Two patients required a second laparotomy for intra-abdominal bleeding shortly after the operation.In one, a bleeding branch of the iliac artery was ligated. The bleeding in the other patient could be explained by mild coagulation disorders on the basis of subclinical hepatitis. In a third patient, too, coagulation disorders were observed immediately after operation, manifested by bleeding in the wound. Careful haemostasis and correction of coagulation led to recovery.
A striking finding was that one patient developed respiratory distress of obscure aetiology, requiring ventilation during three days.

X.3 Other complications

Some of the other complications are unmistakably correlated with the type of operation performed. As already mentioned, chylous ascites results from damage to lymphatics, causing lymph to accumulate in the abdominal cavity. Free fluid is always demonstrable in the abdominal cavity during the first few postoperative weeks. It always disappears spontaneously.
Another complication related to retroperitoneal lymph node dissection is contralateral hydrocele, found in 10 of the 87 patients (11%). The other

complications - respiratory infection, urinary infection and disturbed wound healing - are not specific for retroperitoneal lymph node dissection. They were not frequent and could always be adequately managed.

X.4 Ejaculation disorders

As already pointed out in chapter VII, ejaculation disorders are inherent to retroperitoneal lymph node dissection because this entails damage to the sympathetic trunk. Of the 86 patients treated by bilateral retroperitoneal lymph node dissection, 74 (86%) showed complete loss of ejaculation. In the remaining 12 (14%) there was still some ejaculation. Erection and orgasm were normal in all patients. Three patients fathered children after the operation.
So far, pregnancy has been induced in the partners of two more patients with the aid of imipramine - a sympathicomimetic which can cause antegrade ejaculation (Nijman et al. 1980). Of the 86 patients, 55 (64%) already had children before the operation. Of the remaining 26, who fathered no children either before or after the operation, 15 were in stage I and 11 were in stage II.

X.5 Complications of radiotherapy

Ten patients in stages IIA and IIB who received adjuvant radiotherapy on para-aortic and para-iliac areas and the mediastinum, developed no complications. One stage IIC patient in whom node dissection was impossible and who was therefore irradiated, developed ileus on the basis of intestinal fibrosis after two years. After 12 years, moreover, he required nephroureterectomy for ureteral stenosis. This patient received 2400 rad (24 Gy) on para-aortic and para-iliac areas in 6 weeks, and a boost of 2600 rad (26 Gy) on metastases in the left renal hilus.

X.6 Complications of chemotherapy

The cytostatics given to the patients in the Groningen series were actinomycin-D, vinblastine, bleomycin and cis-platinum. Other agents used sporadically were methotrexate, cyclophosphamide and adriamycin. Most experience has so far been gained with actinomycin-D. The dosage of this agent in these patients was 1 mg per day during 5 days. This course was repeated every six weeks over a period of two years.

Alopecia, stomatitis, nausea and vomiting were observed in virtually all patients. Acne was frequently seen. One patient in stage IIC developed severe thrombocytopenia. Of 10 patients given adjuvant radiotherapy as well as actinomycin-D, two developed severe leucocytopenia, and one severe thrombocytopenia. This necessitated reduction of the actinomycin-D dosage. Another patient in stage I who developed lung metastases, likewise developed thrombocytopenia during combined treatment with actinomycin-D and irradiation. As already mentioned previously, one patient in whom splenectomy had to be performed, developed bacterial meningitis during an adjuvant actinomycin-D course.

In the patients treated with vinblastine and bleomycin according to our dosage scheme, complications were hardly observed. In a few cases the total dose of bleomycin exceeded 350 mg. None of these patients developed the features of interstitial pneumonitis. Pulmonary function tests were performed weekly during bleomycin medication. One patient developed prolonged neuropathy due to vinblastine. Another patient, who received large doses of vinblastine (15 mg per day during five days), developed severe leucocytopenia.

Only five patients were treated with the PVB combination (cis-platinum, vinblastine and bleomycin) during the period studied, and two received cis-platinum in combination with another agent. Five of these seven patients had previously received radiotherapy and/or actinomycin-D medication. Two of the seven died during treatment as a consequence of sepsis, and a third died from myocardial infarction a year after the end of the chemotherapy. Our later experience with cis-platinum has been more fortunate.

X.7 Duration of hospital stay

Although this is not a complication of therapy, the duration of the stay in hospital invites some remarks here because it gives some information on the surgical intervention. It was studied only for the 87 patients treated by retroperitoneal lymph node dissection. The total hospital stay of the stage I patients was 17 (9-79) days, while that of the stage II patients was 18 (7-42) days. Since the mean postoperative hospital stay gives more information on the operation performed, this was determined separately. It was 11 (6-73) days for stage I and 12 (6-36) days for stage II patients. Most stage II patients received the first clinical adjuvant actinomycin-D medication during the same hospital stay.

X.8 Discussion

In the literature, the complication rate of retroperitoneal lymph node dissections ranges from 6.9% to 30% (Staubitz et al. 1974; Johnson et al. 1976; Lindsey and Glenn 1978; Sago et al. 1979). This percentage is dependent on whether only major complications are considered or other complications included as well.
If we disregard one pneumonia and one instance of disturbed wound healing in two patients not treated by node dissection, the complication rate of retroperitoneal lymph node dissection in our series can be reported as 35.6%. Confining ourselves to "major complications", we find a complication rate of 8%. An important finding is that none of the patients died as a result of the operation. On the other hand, ureteral damage necessitating nephrectomy in two cases was a "major complication". Both instances, however, occurred in the early period of retroperitoneal lymph node dissection in our department. Increased experience has since played a role without doubt. Although the complication rate can never be reduced to zero, the morbidity of retroperitoneal lymph node dissection in experienced hands can be described as low. The relatively brief average stay in hospital bears witness to this.

A remarkable finding was the large number of hydroceles developed in the contralateral testis after the operation. The literature comprises no reports on this subject. Possible causes are either venous congestion resulting from the sacrifice of the contralateral spermatic vein or obstruction of lymph drainage due to resection of the lymphatics of the contralateral testis. The hydrocele can be regarded as an expression of oedema.

Sago et al. (1979) found wound infections in 25% of patients whose treatment had included appendectomy, versus 9.5% of those where the appendix was not removed. Although appendectomy was routinely performed in the Groningen series, wound infections were not observed. Routine appendectomy need therefore not be refrained from in view of the risk of infection. The principal rationale of appendectomy is that it facilitates evaluation of an acute abdomen in a previously laparotomized patient.

The side effects of chemotherapy were mild. Admittedly, the stomatitis, acne and alopecia observed in patients given actinomycin-D are severe side effects which unmistakably affect the quality of life (Giel et al. 1977). But it was nevertheless a fact that in particular the patients given actinomycin-D

during two years, ultimately showed good tolerance to this therapy. Most patients even resumed normal work during the intervals between courses. Our series also shows that the combination of chemotherapy and radiotherapy has its risks. Three of the 10 patients given both radiotherapy and actinomycin-D showed a bone marrow reaction which made it necessary to reduce the dosage of the cytostatic. This phenomenon was not observed in the 17 patients who received only adjuvant actinomycin-D.
Similar findings were obtained in patients given cis-platinum, vinblastine and bleomycin after previous radiotherapy (Stoter et al. 1979). In actual fact, therefore, we are dealing with a side effect of irradiation. The implication of this finding is that the choice of treatment - regardless of whether it is primary or adjuvant treatment - always raises the question whether radiotherapy will influence any further treatment.
One patient developed bacterial meningitis during the adjuvant treatment with actinomycin-D. This patient's spleen had to be removed after it had been accidentally damaged in the preceding operation. The meningitis in this patient was undoubtedly related to the absence of the spleen.

Ejaculation disorders developed in all patients. Although some authors (Leiter and Brendler 1967; Johnson 1976) maintain that these are transient disorders, we observed no spontaneous recovery in the Groningen patients. Yet five patients fathered one or more children after the operation. Nijman et al. (1980) reported that antegrade ejaculation could be induced in most cases with the aid of the sympathicomimetic imipramine. In two cases the partners did in fact become pregnant. This is a promising observation.
The fact that 64% of our patients had already fathered children prior to the operation demonstrates the questionally of the statement that patients with a malignant testicular tumour are often infertile. Skinner (1980) found fertile sperm in only 21% (5/24) of the patients after orchiectomy. It should be borne in mind, however, that these patients were men who had recently been orchiectomized and were still in a state of stress. Nevertheless the implication is that, in most cases, semen is unsuitable for refrigerator storage after orchiectomy.
As already mentioned in chapter VI, it makes no difference in ejaculation disorders whether an extensive bilateral or a modified unilateral dissection is performed. In view of the finding (in the Groningen patients) that metastases can also spread to the contralateral para-iliac nodes, we continue to perform extensive bilateral lymph node dissection when metastases are

macroscopically visible. The question remains, however, whether extensive dissection should also be performed when no enlarged retroperitoneal lymph nodes are palpable at laparotomy. It may be sufficient in those cases to dissect the primary lymph node sites on the ipsilateral side, followed by watchful waiting with tumour marker monitoring. A prospective randomized study will have to provide the answer to this question.

CHAPTER XI

THE VALUE OF LYMPHOGRAPHY IN DIAGNOSIS

This chapter considers the value of lymphography as a staging method. As already pointed out, this procedure has its limitations. We have tried to determine its value on the basis of the data on the Groningen patients. As already mentioned in the introduction to chapter VIII, the available lymphograms were all revised by one person (Dr. J. M. H. Blom), who received no information on the case histories.

XI.1 Data on the patients

The lymphograms available on the 103 patients numbered 95, because in some cases no lymphography had been performed or the lymphograms had been lost.

Nine of these 95 lymphograms were rejected because the technical quality was insufficient (only unilateral filling with contrast medium or absence of some exposures, so that evaluation was impossible). The technical imperfections in the older cases were not more marked than those in more recent cases.

The remaining 86 lymphograms were correlated to the histology of the retroperitoneal lymph nodes and/or the findings at operation. Of the 86 patients whose lymphograms were suitable for evaluation, 71 had been treated by bilateral retroperitoneal lymph node dissection. In the remaining 15 cases only exploratory laparotomy had been performed, which revealed inoperable retroperitoneal metastases in 13 cases. Two patients had a solitary liver metastasis without lesions of retroperitoneal lymph nodes.

Of the 71 patients treated by dissection, 46 had histologically normal nodes,

while in 25 metastases were histologically demonstrable. This gave us a total of 48 (46 + 2) patients with negative, and 38 (25 + 13) patients with positive lymph nodes.

XI.2 Results

The lymphograms of 25 patients were interpreted as abnormal, and in 22 (88%) of these cases the retroperitoneal nodes proved to be histologically positive as well. The lymphograms of 61 patients were interpreted as normal, and in 45 (74%) of these cases this proved to be in agreement with the histology of the findings at laparotomy (see table XI.1).

histology/ peroperative findings		negative lymphography	positive lymphography
no metastases	48	45	3
metastases	38	16	22
total	86	61	25

Table XI.1: Reliability of lymphography.

The accuracy of lymphography in the entire group of 86 patients was found to be 78%. Separately considering the group of patients with retroperitoneal lymph node metastases, we find that these metastases were lymphographically demonstrable in only 22 of the 38 patients (58%). Four of the 38 patients with histologically abnormal nodes proved to have only micrometastases. In two cases the lymphogram was interpreted as abnormal, and in the other two it was considered normal. Node size in these four cases ranged from 0.5 cm to 1 cm.

The lymphograms of the 13 patients with inoperable retroperitoneal metastases were all correctly interpreted, with one exception. Of the lymphograms of the remaining 25 patients in stage II, 10 (40%) were correctly interpreted, while the remaining 15 were false negative.

On the basis of the pathological findings, the correlation between lymphogram interpretation and node size was studied, accepting the diameter of the largest node as standard. For the 13 inoperable patients we proceeded from a node size of 5 cm or more. The correlation between lymphographic accuracy and node size is shown in table XI.2 and figure XI.1. No correlation was demonstrable between lymphographic findings and microscopic growth of tumour cells through the lymph node capsule.

node size	accuracy
$\leqslant$ 1 cm	25 % (1/4)
$1 < x \leqslant 2$ cm	28.6% (4/14)
$2 < x \leqslant 5$ cm	71.4% (5/7)
> 5 cm	92.3% (12/13)

Table XI.2: Reliability of lymphography in relation to node size.

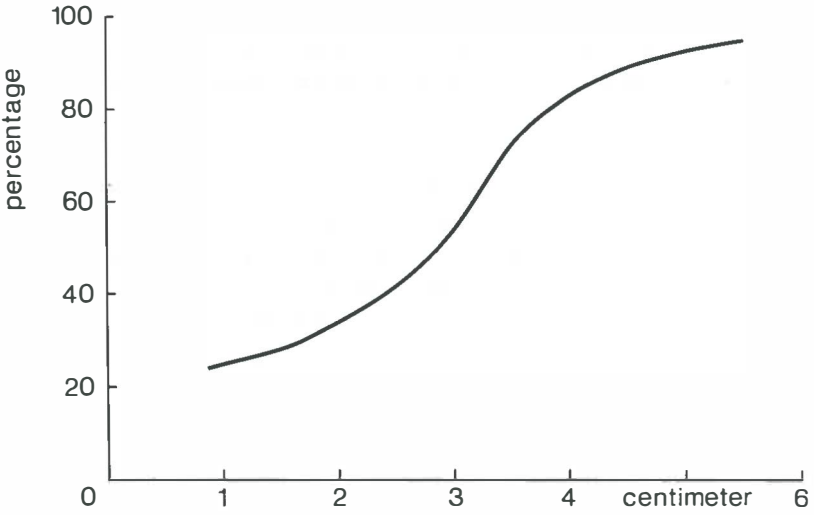


Fig. XI.1 Reliability in relation to the size of the lymph nodes.

The correlation between lymphographic findings and the various substages in our staging system was likewise studied. A survey of the findings is presented in table XI.3.

	lymphography	
	abnormal	normal
stage IIA n = 10	2 (20%)	8 (80%)
stage IIB n = 15	8 (53%)	7 (47%)
stage IIC n = 13	12 (92%)	1 (8%)

Table XI.3: Lymphographic findings related to histological staging and peroperative findings.

We found that 80% of lymphograms in histological stage IIA had been false negative; in stage IIB the chances of correct and incorrect interpretation were about equal. In stage IIC, virtually all patients had been correctly staged on the basis of the lymphogram.

XI.3 Comparison of therapeutic results according to staging method

In an effort to establish whether the staging method exerts any influence on therapeutic results, we determined the 3-year survival of a given group of patients, staged on the basis of lymphography on the one hand, and on the basis of findings at operation and/or histological examination on the other hand. The two patients with inguinal lymph node metastases were excluded from this study, leaving 84 of the 86 patients on whom lymphograms were available.

Of these 84 patients, 59 were in stage I and 25 in stage II according to lymphographic findings. Histological staging of the same group placed 45 patients in stage I, 37 in stage II and 2 in stage III. The 3-year survival was 90% (53/59) in lymphographic stage I and 64% (16/25) in lymphographic stage II. In the histological stages, 3-year survival was 98% (44/45) in stage I, 59% (22/37) in stage II and 100% (2/2) in stage III (table XI.4).

	3-year survival	
	after lymphographic staging	after histological staging/laparotomy
stage I	53/59 (90%)	44/45 (98%)
stage II	15/25 (64%)	22/37 (59%)
stage III	—	2/2 (100%)

Table XI.4: Comparison of 3-year survival rates after lymphographic and after histological staging.

XI.4 Discussion

The observation that the lymphogram is most reliable when interpreted as abnormal (88%) confirms reports by other authors (see table IV.1). Reliability of lymphograms interpreted as normal was significantly lower (74%). In our series of patients, lymphographic identification of lymph node metastases proved to be even less reliable.

Metastases were on lymphography demonstrated in only 22 of the 38 patients (58%) in this series.

Our findings also reveal a correlation between size of lymph node metastases and lymphogram reliability (table XI.2). In only one of the 13 cases in which lymph node metastases were too extensive to permit dissection was the lymphogram interpreted as negative. We also established a positive correlation between lymphogram reliability and substages II (table XI.3).

This findings do not corroborate the observation of Fein and Taber (1969) that only abnormal nodes with a diameter of 2 cm or more can be lymphographically demonstrated. The two lymphograms interpreted as abnormal in patients with histological micrometastases demonstrate that even minimal lesions can be detected. We therefore accept no particular lymph node size as minimum size required to make lymphographic demonstration possible.

However, the fact that 80% of the metastases in stage IIA were overlooked warrants the conclusion that it is particularly the smaller metastases that are not detected by lymphography.

In no case did we see the fibrotic reaction around the lymph nodes believed to be caused by the oily contrast medium (Skinner 1976), and thought to impede lymph node dissection. Perhaps this is to do with the interval between lymphography and retroperitoneal lymph node dissection, which in our department is usually only a few days. The reaction around the lymph nodes therefore does not seem to contraindicate lymphographic examination. The advantage of lymphography is that a peroperative plain abdominal X-ray can be used to establish whether all nodes containing contrast medium have been removed. Another advantage is that regression of lymph node metastases can be monitored during and after chemotherapy when the nodes prove to be inoperable at laparotomy. For the latter purpose, however, the CT-scan seems to be about to replace lymphography (Husband et al. 1979, 1981).

In the literature we found no reports relating therapeutic results to staging method. Our figures would seem to lead to the conclusion that the results in stage I are slightly less good when lymphographic staging is done. This is not surprising when we realize that precisely lymphograms interpreted as negative are least reliable. In our series of patients this was 74%, which means that this group includes several cases in which metastases are in fact present. For stage II a difference, if any, is far less evident. This is in agreement with the fact that only 12% of the lymphograms were falsely interpreted as positive.

In considering the value of lymphography in the diagnosis of non-seminomatous testicular tumours it should be borne in mind that the method fails in a number of cases. We found in our series that the lymphogram was of insufficient technical quality in 9 cases (9%); in these cases, therefore, there was in fact no preoperative information on the retroperitoneal lymph nodes. The CT-scan cannot entirely replace lymphography. As already pointed out in chapter V, lymphography and CT-scan are complementary procedures. We are thus using a diagnostic procedure with limitations, and consequently the basis of clinical staging is uncertain.

It can be stated in conclusion that the reliability of lymphography in the diagnosis of non-seminomatous testicular tumours is limited. Staging on the basis of lymphographic findings is consequently of only relative value. The most reliable method of staging non-seminomatous testicular tumours is laparotomy and - if possible - retroperitoneal lymph node dissection for histological determination of the number and size of metastases.

CHAPTER XII

THE PROGNOSTIC SIGNIFICANCE OF THE LOCAL EXTENT OF THE PRIMARY TUMOUR

XII.1 Introduction

The literature presents few data on the significance of the local extent of the primary tumour for the ultimate prognosis. Patients with a large primary tumour extending into the testicular appendages or into the spermatic cord can be expected to have a less favourable prognosis. With advanced primary tumour growth, moreover, metastases are more likely; and consequently it is not surprising that prognostic significance is generally attached to these metastases as well.

Most staging systems for malignant testicular tumours describe the primary tumour in stage I as limited to the testis or its appendages (Johnson 1976; Fraley et al. 1980; Skinner and Scardino 1980). An exception is the TNM classification of the UICC (1979), which is also used by the American Joint Committee (1977). In this system the primary tumour is divided into several substages according to its local extension. This staging system, however, has been a subject of discussion in recent years (Sandeman and Matthews 1979; Batata et al. 1980; Prout 1980; Cavalli et al. 1980). The crucial question in this respect is whether dividing the primary tumour into various categories as in the TNM classification has therapeutic and prognostic implications. We have attempted to form an opinion on this question on the basis of the histological data on the Groningen patients.

XII.2 Methods of investigation

For primary tumour staging we proceeded from the TNM classification of

the UICC (1979). The TNM system is a clinical staging system, but pathological data can be taken into account in it, in which case it is referred to as pTNM classification. The symbol T for the primary tumour can also be replaced by a P to indicate this. When we mention the various P categories in this study we are always referring to the postoperative histopathological classification P.
Table XII.1 presents a survey of primary tumour staging as proposed by the UICC (1979). It was found (table XII.2) that 48 of the 103 patients had a stage P1 tumour; P2 existed in 3, P3 in 48, and P4 in 4 cases (P4a in 2 and P4b in 2).

P0	no evidence of a primary tumour
P1	tumour limited to the body of the testis
P2	tumour extending beyond the tunica albuginea
P4	tumour involving the rete testis or epididymis
P4	tumour invading the spermatic cord or scrotum wall
	P4a invasion of the spermatic cord
	P4b invasion of the scrotum wall

Table XII.1: Staging system of the primary tumour according to the UICC (1979).

In order to establish whether the local extent of primary tumour influences the prognosis, it has to be correlated to regional lymph node involvement as well as to distant metastases. In addition we have correlated the staging of the primary tumour to survival, although in most cases this is partly influenced also by therapy. We accepted the presence of organ metastases (lungs, liver) as criterion for distant metastatic growth.
Table XII.2 presents data on the correlation found between P category on the one hand, and stage found at laparotomy, retroperitoneal lymph node dissection or inguinal lymph node dissection (see table VII.2). The two patients with inguinal lymph node metastases were classified in stage IIB because the histological features of the metastases fulfilled the stage IIB criteria.
Category P2 was found in only three stage I patients. Considering the P1 and P2 categories together, we find that 35 of the 54 stage I patients (65%) had a tumour confined to the testis. In 33% of the stage I patient the tumour extended into the testicular appendages. Only one patient showed extension of the tumour into the spermatic cord; this patient later developed a local recurrence in the inguinal region.

		P0	P1	P2	P3	P4a	P4b
stage I	n = 54	—	32 (59%)	3	18 (33%)	1	—
stage IIA	n = 13	—	6 (46%)	—	7 (54%)	—	—
stage IIB	n = 20	—	6 (30%)	—	11 (55%)	1	2
stage IIC	n = 14	—	3 (21%)	—	11 (78%)	—	—
stage III	n = 2	—	1	—	1	—	—
total	n = 103		48 (47%)	3	48 (47%)	2	2

Table XII.2: Correlation between P categories and postoperative stages.

No distinct difference in distribution of the various P categories was found in stage IIA (46% versus 54%). The difference was more pronounced in stages IIB and IIC. The numbers for stage III were too small to permit comparison.

Table XII.3 presents data on the correlation between P category and development of organ metastases. Organ metastases developed in 10% (5/48) of patients whose tumour was confined to the testis, versus 33% (16/48) of patients whose tumour had extended into the testicular appendages. Of the two patients in category P4a, one developed lung metastases.

	number of patients with organ metastases	P0	P1	P2	P3	P4a	P4b
stage I	5	—	1	—	3	1	—
stage IIA	3	—	1	—	2	—	—
stage IIB	4	—	1	—	3	—	—
stage IIC	8	—	1	—	7	—	—
stage III	2	—	1	—	1	—	—
total	22		5		16	1	

Table XII.3: Correlation between P categories and development of organ metastases.

Table XII.4 indicates the correlation between P category and mortality. Since in our series the development of organ metastases led to a fatal issue in the majority of cases, there are hardly any differences between the figures in table XII.3 and those in table XII.4. The mortality was 6% (3/48) in the patients with category P1, and 30% (15/48) in those with category P3.

	number of deceased patients	P0	P1	P2	P3	P4a	P4b
stage I	2	—	—	—	1	1	—
stage IIA	3	—	1	—	2	—	—
stage IIB	4	—	—	—	4	—	—
stage IIC	10	—	2	—	8	—	—
stage III	0	—	—	—	—	—	—
total	19		3		15	1	

Table XII.4: Correlation between P categories and mortality.

Another question studied was whether tumour invasion into blood vessels and lymphatics influenced the development of organ metastases (table XII.5). Organ metastases were found in 38% of patients in whom histological examination revealed invasion of the primary tumour into blood vessels and lymphatics, versus 13% of patients in whom this was not the case.

	infiltration in blood vessels and lymphatics	no infiltration in blood vessels and lymphatics
	34/103 (33%)	69/103 (76%)
organ metastases	13/34 (38%)	9/69 (13%)
mortality	13/34 (38%)	6/69 (9%)

Table XII.5: Correlation between development of organ metastases, mortality and infiltration in blood vessels and lymphatics.

It was finally found that, in stage I, tumour invasion into blood vessels and lymphatics was found in 20% (11/54) of patients, versus 42% (14/33) in stages IIA and IIB and 64% (9/14) in stage IIC (table XII.6).

		infiltration in blood vessels and lymphatics		organ metastases	deaths
stage I	n = 54	11 (20%)		2 (18%)	2 (18%)
stage IIA	n = 13	4 (31%)	42%	1 (25%)	1 (25%)
stage IIB	n = 20	10 (50%)		2 (20%)	2 (20%)
stage IIC	n = 14	9 (64%)		6 (67%)	8 (89%)
stage III	n = 2	0		2	0

Table XII.6: Correlation between development of organ metastases, mortality and infiltration in blood vessels and lymphatics for the various substages.

Of patients with tumour invasion into blood vessels and lymphatics, 18%, 25%, 20% and 67% developed organ metastases in stages I, IIA, IIB and IIC, respectively. A conspicuous finding was that the histological specimen of the primary tumour showed no invasion into blood vessels and lymphatics in the two patients in stage III (liver metastases).

XII.3 Discussion

As already pointed out in section V.5, a staging system should have a function in therapy and in determining the prognosis. In malignant testicular tumours, possible spread of the tumour to the retroperitoneal lymph nodes has always been regarded as the principal prognostic parameter. In addition we know that the histology of the primary tumour is also important. The question is whether the local extent of primary tumour is likewise of significance for treatment and prognosis.

Several publications in the past few years have considered the value of staging the primary tumour (Sandeman and Matthews 1979; Batata et al. 1980). Both groups of investigators reached the conclusion that the TNM system contributed nothing new to primary tumour staging.

Which conclusion is justifiable on the basis of our personal observations? The finding that the P2 category has a low incidence (3%) has also been reported by other authors. Batata et al. (1980) found the P2 category in only 0.8% of patients, while Sandeman and Matthews (1979) reported it in 2%. We conclude from this that the P2 category (extension of tumour beyond the tunica albuginea) has a low incidence and is of no significance. Strikingly, the P3 category was as frequently found as the P1 category in our series (47%). Sandeman and Matthews (1979) reported a P3 incidence of 6%, and Batata et al. (1980) reported 2%. The cause of these marked differences from the literature has remained obscure. Inaccuracies in histological examination could hardly account for them.

Considering the various P categories in relation to retroperitoneal lymph node involvement (table XII.2), we find that P1 and P2 are quite common in stage I (65%) and that P3 shows an increasing incidence in the various substages II. This would seem to infer that the P1 and P2 categories are more favourable than P3 - an implication which merely confirms that stage I is less unfavourable than stage II, and that stage IIA is less unfavourable than stage IIC. The conclusion is that the primary tumour subdivision into P categories correlates with the traditional staging system but is not more exact.

Considering the correlation between the various P categories on the one hand, and development of organ metastases and mortality on the other, the latter parameters both seem to be slightly more common in the P3 category. For stages I, IIA and IIB, however, the numbers are too small to warrant conclusions. More specifically, it cannot be established whether in stage IIA organ metastases are more common when the primary tumour extends into the testicular appendages or into blood vessels and lymphatics. This might have therapeutic implications. In stage IIC the P3 category seems to be unmistakably unfavourable factor in terms of organ metastases and mortality. It should be borne in mind, however, that in all these cases retroperitoneal lymph node dissection was impossible. Dissemination to the organs may therefore equally well have taken place from these metastases.

As expected, invasion of the primary tumour into blood vessels and lymphatics proved to be an unfavourable factor. Organ metastases were found in 38% of patients showing such tumour invasion, versus 13% of those who did not (table XII.5). This phenomenon also proved to exert an unmistakable influence on the ultimate prognosis. Of the 34 patients with this type of tumour extension, 13 (38%) died, versus only 6 of the remaining 69 patients (9%). Moreover, a correlation was also found between tumour invasion into blood vessels and lymphatics, and retroperitoneal lymph node involvement (table XII.6). Considering the extent to which this influenced development of organ metastases, we must conclude that this was the same in stages I, IIA and IIB. In stage IIC, however, invasion of tumour into blood vessels and lymphatics was associated with a higher incidence of organ metastases and a higher mortality. It should again be borne in mind that tumour tissue was still in situ in the retroperitoneum in all these cases.
We might conclude that invasion of the primary tumour into blood vessels and lymphatics is more likely related to lymphogenous than to haematogenous dissemination, although this seems contradictory. In that case haematogenous dissemination should be regarded more as a sequel of lymphogenous dissemination than as primary tumour dissemination. That primary haematogenous dissemination of malignant testicular tumours is possible is demonstrated by the two patients in whom laparotomy revealed only liver metastases. But in these two cases no primary tumour was found in blood vessels and lymphatics. We must bear in mind that detection of such tumour in blood vessels and lymphatics is largely dependent on the number of sections cut. A limited examination of the primary tumour affords but a low chance of detection (Sandeman and Matthews 1979).

The figures obtained warrant no conclusion about categories P4a and P4b. Theoretically, these would seem to be unfavourable categories. Sandeman and Matthews (1979) in fact regard them as so unfavourable that they propose classification of tumours with these characteristics as T2, versus T1 for all other categories.

In view of these findings we feel it is justifiable to conclude that the local extent of primary tumour, as symbolized by the various P categories, and primary tumour invasion in blood vessels and lymphatics, are reflected in the involvement of the retroperitoneal lymph nodes. We therefore see no need to subdivide into various T or P categories according to the TNM classification. In this respect we agree with Batata et al. (1980) and Cavalli et al. (1980).

In actual practice, a staging system based on the retroperitoneal lymph nodes provides a more exact guideline for treatment in stages I and II. It should be realized, however, that a tumour confined to the testis generally has a more favourable prognosis than one that has invaded adjacent structures. For the time being, this finding does not seem to have any therapeutic implications. When no laparotomy or retroperitoneal lymph node dissection is performed for staging, data on the primary tumour may indeed contribute to the choice of therapy.

SUMMARY AND CONCLUSIONS

This thesis presents and discusses the results of a retrospective study of 103 patients with a non-seminomatous germ cell tumour of the testis in clinical stages I and II, treated in the Division of Surgical Oncology of the Department of Surgery, University Hospital, Groningen, over the period 1963 through 1977. Laparotomy was performed in all these cases, with retroperitoneal lymph node dissection if possible.

Chapter I defines the objectives of this study.

Chapter II presents a general survey of data on malignant testicular tumours.

Chapter III discusses the mode of metastatic spread of these neoplasms, with special reference to the lymph drainage system of the testis.

Chapter IV deals with the various types of investigative procedures, which are important in the diagnosis of malignant tumours of the testis, with special reference to the retroperitoneal metastases.

Chapter V reviews the principal histological classifications of malignant testicular tumours and discusses some staging systems.

Chapter VI discusses various methods of treatment of non-seminomatous tumours of the testis. A review of historical developments is followed by a description of surgical and radiotherapeutic methods. A survey of chemotherapy is presented, and a few chemotherapy programmes are discussed in detail.

Chapter VII describes the operative techniques of transabdominal bilateral retroperitoneal lymph node dissection and thoraco-abdominal retroperitoneal lymph node dissection, with special reference to complications of these operations.

Chapter VIII presents the general data on our series of 103 patients with a non-seminomatous germ cell tumours of the testis in the clinical stages I and II, using the histological classification proposed by Dixon and Moore (1953). Of these 103 patients, 35 had an embryonal carcinoma, 13 a malignant teratoma, 51 a combination of embryonal carcinoma and teratoma (teratocarcinoma), and 4 a choriocarcinoma. In all these patients, detailed examinations revealed no metastases cranial to the diaphragm (stages I and II). Retroperitoneal lymph node dissection was feasible in 87 patients (transabdominal in 86, and thoraco-abdominal in 1).

In 14 patients it was found impossible to remove the retroperitoneal metastases. Two had a solitary liver metastasis without palpable lesions of the retroperitoneal lymph nodes. In two others, with a history of orchiopexy, inguinal lymph node metastases were found as well. In these two cases inguinal lymph node dissection was performed in addition.

Using the staging system as mentioned by Skinner and Scardino (1980), 54 patients were included in stage I (negative retroperitoneal lymph nodes), 13 in stage IIA (fewer than six metastases, less than 2 cm in diameter, without infiltration of adjacent tissues), 20 in stage IIB (node metastases numbering six or more *or* more than 2 cm in diameter *or* infiltration of adjacent tissues), 14 in stage IIC (bulky disease) and 2 in stage III (organ metastases).

With regard to the distribution of the retroperitoneal metastases, cross-over was found in 7 of 19 patients (37%) with a right-sided, and in 4 of 13 (31%) with a left-sided tumour. Five patients (5%) had a history of orchiopexy for undescended testicle. Seven (7%) had a history of an inguinal hernia operation or showed an inguinal hernia at the time of orchiectomy.

The findings warrant the conclusion that bilateral retroperitoneal lymph node dissection is imperative when retroperitoneal lymph node metastases are found. Additional inguinal lymph node dissection is indicated when there is an inguinal operation in the history, because in such cases metastasis to inguinal lymph nodes can occur as a result of a change in lymph drainage.

Chapter IX explains the methods of treatment and discusses therapeutic results. In stage I (54 patients) retroperitoneal lymph node dissection was not followed by any other therapy; 5 of these patients (9%) developed lung metastases after 5-16 months, and 1 patient (2%) developed a contralateral para-iliac tumour. The 3-year survival in stage I was 96% (52/54) and recurrence-free survival was 89% (48/54). In view of these results, we maintain that no adjuvant therapy is indicated in stage I.

In stages IIA and IIB, adjuvant therapy after retroperitoneal lymph node dissection has changed in the course of the years. During the period 1963-1968, no adjuvant therapy was given. Of the 4 patients treated by retroperitoneal lymph node dissection only, 2 (50%) developed lung metastases and both died.

During the period 1968-1974, 10 patients received radiotherapy (3000 rad (30 Gy) in 3 weeks on para-aortic, iliac and mediastinal areas, and a boost of 2000 rad (20 Gy) on the site from which retroperitoneal metastases had been removed) as well as chemotherapy (1 mg actinomycin-D per day during 5 days, every six weeks). Lung metastases developed in 3 of the 10 patients so treated (30%). This group had a 3-year and 5-year survival of 80%, and a recurrence-free survival of 70%.

From 1975 on, only actinomycin-D was given as adjuvant chemotherapeutic agent. Of the 16 patients (14 with retroperitoneal and 2 with inguinal lymph node metastases) so treated, one developed lung metastases. The 3-year survival was 94% (15/16); recurrence-free survival was the same. For various reasons, three patients received only radiotherapy after node dissection; one developed lung metastases and one developed supraclavicular metastases, and both died within three years. The 3-year survival for the entire group of patients in stage IIA and IIB was 79% (26/33); recurrence-free survival was 76% (25/33).

Of the 26 (16 + 10) patients with loco-regional lesions given adjuvant therapy with actinomycin-D (alone or in combination with radiotherapy) 4 (15%) developed lung metastases. Of the 7 patients given only radiotherapy or no further treatment after node dissection, 3 (43%) developed lung metastases and 1 developed supraclavicular metastases.

In view of the results obtained in the patients in stages IIA and IIB we hold that adjuvant radiotherapy is not required, because recurrence is nearly always found in the lungs. Actinomycin-D in the programme we used has proved to be an effective adjuvant drug, and was well tolerated by all patients.

Treatment of the 14 patients in stage IIC consisted of a combination of surgery, radiotherapy and chemotherapy. In principle, actinomycin-D was regarded as the cytostatic of choice. When it remained ineffective, it was replaced by vinblastine and bleomycin. Of these 14 patients, five received cis-platinum, vinblastine and bleomycin. Only three of the 14 patients (21%) remained clinically free of metastases for a considerable length of time.

The two patients with a liver metastasis survived 10 years and 7 years, respectively, without evidence of tumour growth. One received local irradiation, and the other was treated by local excision followed by two years of actinomycin-D medication.
A study of the results revealed that the actinomycin-D programme we used led to partial remission in only 31% (5/16) of the patients with extensive tumour growth and in 12.5% (2/16) to a complete remission.

Chapter X discusses the complications of therapy, dividing them into "major complications" and "other complications". There was no mortality due to therapy. The major complications included a ureteral lesion (necesitating nephrectomy) in two cases, and accidental injury of the spleen in one case. Under this heading we also include two instances of postoperative haemorrhage necessitating a second laparotomy, a case with coagulation disorders, and a case of distress syndrome.
The "other complications" were generally complications of a type that can develop after any laparotomy.
Nearly all patients treated by retroperitoneal lymph node dissection developed ejaculation disorders.
The mean stay in hospital of the stage I patients was 17 days; that in stages IIA and IIB was 18 days. The mean stay in hospital after retroperitoneal lymph node dissection was 11 and 12 days, respectively, in these two groups.

Chapter XI discusses the significance of lymphography in the diagnosis of retroperitoneal lymph node metastases. All available lymphograms were revised. Of the 95 lymphograms available, 86 were suitable for the purposes of this study. Correlation with operative and/or histological findings revealed 78% reliability. The reliability of lymphograms interpreted as abnormal was 88%, versus 74% for those considered to be normal.
Retroperitoneal lymph node metastases were identified with the aid of lymphography in 58% of patients. We found no lymph node size limit above which metastases could be lymphographically demonstrated with certainty. We found no differences in therapeutic results in correlation with the method of staging.
Our conclusion is that lymphography is of only limited value in the diagnosis of non-seminomatous germ cell tumours of the testis.

Chapter XII considers the question whether the local extension of the primary tumour exerts an influence on distant metastatic spread and prognosis.

Proceeding from the TNM classification, we found that tumours not extending beyond the tunica albuginea (P1 and P2) were more frequent in stage I (65%) than those extending into the testicular appendages (P3; 33%). In this respect no differences were found in stage IIA, but in stages IIB and IIC the P3 category was found in 55% and 78% of cases, respectively. Of the 22 patients with organ metastases, 2 (23%) showed category P1, 16 (73%) category P3 and 1 (4%) category P4a. Similar figures were obtained in relation to survival. Category P1 was associated with organ metastases in 10% (5/48) of cases, and category P3 in 33% (16/48).

Although the local extension of the primary tumour is correlated with the development of lung metastases, we hold that the subdivision of primary tumours proposed by the UICC (1979) is not needed because the incidence of organ metastases shows a similar correlation with retroperitoneal dissemination. A staging system based solely on the retroperitoneal lymph node metastases is therefore quite adequate.

A correlation was established also between tumour infiltration of blood vessels and lymphatics, and the development of organ metastases. Organ metastases developed in 38% of patients with, versus 13% of those without such infiltration. However, nearly 50% of the patients with organ metastases were in stage IIC, and precisely in these patients retroperitoneal tumour tissue was always present from which metastases may have arisen. Finally, a correlation was found between tumour infiltration of blood vessels and lymphatics, and the extension of the retroperitoneal metastasis. Even this, however, does not force us always to regard this phenomenon as a separate unfavourable factor.

We maintain that the condition of the retroperitoneal lymph nodes provides the most rational basis for the staging of non-seminomatous testicular germ cell tumours. The only reliable method to determine this condition is laparotomy and, if possible, retroperitoneal lymph node dissection.

SAMENVATTING EN CONCLUSIES

In dit proefschrift worden de resultaten beschreven van een retrospectief onderzoek bij 103 patienten met een niet-seminoom kiemceltumor van de testis in de klinische stadia I en II, die in de jaren 1963 tot en met 1977 werden behandeld in de afdeling Chirurgische Oncologie van het Academisch Ziekenhuis te Groningen. Al deze 103 patienten ondergingen een laparotomie en zo mogelijk een retroperitoneale lymfeklierdissectie.

In **Hoofdstuk I** worden de doelstellingen van dit onderzoek beschreven.

In **Hoofdstuk II** wordt een algemeen overzicht gegeven over de maligne testistumoren.

De wijze waarop deze gezwellen metastaseren wordt in **Hoofdstuk III** besproken. Speciale aandacht krijgt het lymfeafvloedsysteem van de testis.

In **Hoofdstuk IV** worden de verschillende onderzoekmethoden behandeld, die een rol spelen in de diagnostiek van niet-seminoom testistumoren. Met name krijgt de diagnostiek van de retroperitoneale lymfeklieren de aandacht.

In **Hoofdstuk V** wordt een overzicht gegeven van de belangrijkste histologische klassificaties. Tevens worden enkele methodes genoemd om maligne testistumoren in te delen naar stadium.

De behandelingsmethoden van de niet-seminoom kiemceltumoren van de testis worden in **Hoofdstuk VI** besproken. Na een beschrijving van historische ontwikkelingen komen achtereenvolgens de chirurgische en radiotherapeutische behandelingswijzen aan de orde. Er wordt een overzicht gegeven van de behandeling met chemotherapeutica, waarvan enkele schema's worden genoemd.

In **Hoofdstuk VII** worden de operatietechnieken beschreven van de transabdominale bilaterale retroperitoneale lymfeklierdissectie en de thoracoabdominale retroperitoneale lymfeklierdissectie. De mogelijke complicaties van deze operaties worden besproken.

In **Hoofdstuk VIII** worden de algemene gegevens vermeld van de 103 patienten met een niet-seminoom kiemcel van de testis in de klinische stadia I en II. De gebruikte histologische klassificatie is die van Dixon en Moore (1953). Van deze 103 patienten hadden 35 een embryonaalcelcarcinoom, 13 een maligne teratoom, 51 een combinatie van embryonaalcelcarcinoom en teratoom (teratocarcinoom) en 4 een choriocarcinoom. Allen bleken na uitgebreid onderzoek geen metastasen craniaal van het diafragma te hebben (stadium I en II). Het was bij 87 patienten mogelijk een retroperitoneale lymfeklierdissectie uit te voeren (86 transabdominaal, 1 thoracoabdominaal).
Bij 14 patienten bleken de retroperitoneale metastasen niet te verwijderen. Twee bleken solitaire levermetastasen te hebben, zonder palpatoir afwijkende retroperitoneale lymfeklieren. Bij twee andere patienten, die in het verleden een orchidopexie ondergingen, werden tevens lieskliermetastasen aangetroffen. In deze twee gevallen werd bovendien een liesklierdissectie verricht.
Gebruik makend van de stadiumindeling van Skinner en Scardino (1980) werden 54 patienten ingedeeld in stadium I (negatieve retroperitoneale lymfeklieren), 13 in stadium IIA (kliermetastasen kleiner dan 2 cm, minder dan 6 in aantal, zonder doorgroei in de omgeving), 20 in stadium IIB (kliermetastasen groter dan 2 cm of meer dan 6 in aantal of klieren met ingroei in omgeving), 14 in stadium IIC (bulky disease) en 2 in stadium III (orgaanmetastasen). Wat betreft de verdeling van de retroperitoneale metastasen werd het verschijnsel cross-over bij rechtszijdige tumoren bij 7 van de 9 (37%) patienten gevonden, bij linkszijdige tumoren bij 4 van de 13 (31%). Bij 5 patienten (5%) had in het verleden een orchidopexie plaats gevonden wegens een niet ingedaalde testis. Bij 7 (7%) was er een liesbreukoperatie in de voorgeschiedenis of werd op het moment van de semicastratie een liesbreuk vastgesteld.
Op grond van de bevindingen kan worden geconcludeerd, dat een bilaterale klierdissectie moet worden uitgevoerd, indien er retroperitoneale lymfekliermetastasen worden aangetroffen. Tevens is een liesklierdissectie geindiceerd, indien in het verleden een operatie in de lies heeft plaatsgevonden,

omdat dan door verandering van lymfedrainage metastasering naar de liesklieren kan optreden.

In **Hoofdstuk IX** worden de behandelingsmethoden uiteengezet en de resultaten van de therapie besproken. In stadium I (54 patienten) volgde na de retroperitoneale lymfeklierdissectie geen verdere behandeling. Bij 5 van hen (9%) ontstonden in een tijdsverloop van 5 tot 16 maanden longmetastasen, bij 1 patient (2%) ontwikkelde zich heterolateraal een parailiacaal gelegen tumor. De 3-jaarsoverleving in stadium I is 96% (52/54), de „recurrence-free survival" 89% (48/54). Op grond van deze resultaten menen wij, dat in stadium I geen adjuvans behandeling is aangewezen.
Voor de patienten in stadium IIA en IIB is de adjuvans therapie na de retroperitoneale lymfeklierdissectie in de loop der jaren veranderd. Van 1963 tot 1968 werd volstaan met een retroperitoneale lymfeklierdissectie. Van de vier patienten die op deze wijze werden behandeld, kregen er 2 (50%) longmetastasen; beiden zijn overleden. In de periode 1968 tot 1974 kregen 10 patienten zowel radiotherapie (3000 rad (30 Gy) in 3 weken paraaortaal, iliacaal en mediastinaal en 2000 rad (20 Gy) als boost op de plaats waar de retroperitoneale metastasen werden verwijderd) als chemotherapie (actinomycine-D, 1 mg per dag gedurende 5 dagen om de 6 weken). Bij de 10 op deze wijze behandelde patienten ontwikkelden zich bij 3 (30%) longmetastasen. De 3- en 5-jaarsoverleving van deze groep is 80%, de „recurrence-free survival" 70%.
Vanaf 1975 werd alleen actinomycin-D toegediend als adjuvans chemotherapeuticum. Van de 16 patienten (14 met retroperitoneale en 2 met lieskliermetastasen), die op deze wijze werden behandeld, kreeg één longmetastasen. De 3-jaarsoverleving is 94% (15/16); dit is tevens de „recurrence-free survival".
Drie patienten werden om verschillende redenen na de operatie alleen bestraald. Van deze drie kreeg één longmetastasen en één supraclaviculaire metastasen. Beide patienten overleden binnen drie jaar. De 3-jaarsoverleving van de gehele groep patienten in stadium IIA en IIB is 79% (26/33); de „recurrence-free survival" is 76% (25/33).
Van de 26 patienten (16 + 10) met locoregionale afwijkingen, die onder andere of alleen actinomycine-D als adjuvans behandeling kregen, ontwikkelden er 4 (15%) longmetastasen. Van de 7 patienten, die na de klierdissectie alleen radiotherapie of geen verdere behandeling kregen, ontstonden bij 3 (43%) longmetastasen en bij 1 patient supraclaviculaire metastasen.

Op grond van de resultaten van de behandeling van de patienten in stadium IIA en IIB menen wij, dat radiotherapie niet nodig is als adjuvans behandeling. Het recidief wordt immers vrijwel steeds in de longen aangetroffen. Actinomycin-D in het door ons gegeven schema is een effectief middel gebleken als adjuvans chemotherapeuticum en werd door alle patienten goed verdragen.
Bij de 14 patienten in stadium IIC bestond de behandeling uit een combinatie van chemotherapie, radiotherapie en chirurgie. In principe werd actinomycine-D als cytostaticum van eerste keus beschouwd. Indien met het middel geen effect werd bereikt, werd het vervangen door vinblastine en bleomycine. Van deze 14 patienten kregen vijf een behandeling met cisplatinum, vinblastine en bleomycine. Slechts 3 van de 14 (21%) zijn langdurig zonder klinische aanwijzingen voor metastasen gebleven. De 2 patienten met levermetastasen overleefden respectievelijk 10 en 7 jaar zonder aanwijzingen voor tumorgroei. De ene patient werd locaal bestraald, de andere kreeg na locale excisie gedurende twee jaren actinomycine-D.
Bij de bestudering van de resultaten bleek, dat actinomycine-D slechts bij 31% (5/6) van de patienten met uitgebreide tumorgroei een partiele remissie kon bewerkstelligen, en bij 12.5% (2/16) een volledige remissie. Van vinblastine en bleomycine in het door ons gebruikte schema werd slechts gering effect gezien.

In **Hoofdstuk X** worden de complicaties van de behandeling besproken. Deze worden verdeeld in „belangrijke complicaties" en „andere complicaties". Er was geen mortaliteit. Onder „belangrijke complicaties" werden gerekend twee gevallen van laedering van een ureter (met nefrectomie tot gevolg) en een accidentele miltbeschadiging. Ook rangschikten wij hieronder twee gevallen van nabloeding, waarvoor opnieuw een laparotomie moest worden verricht, een geval van stollingsstoornissen en een geval van „distress syndroom".
Tot de „andere complicaties" rekenden wij in het algemeen de complicaties, die zich na iedere laparotomie kunnen voordoen.
Bij vrijwel alle patienten, die een retroperitoneale lymfeklierdissectie ondergingen, werden ejaculatiestoornissen gevonden.
De gemiddelde opnameduur van de patienten in stadium I was 17 dagen, en in stadium IIA an IIB 18 dagen. De gemiddelde opnameduur na de retroperitoneale lymfeklierdissectie was voor beide groepen van patienten respectievelijk 11 en 12 dagen.

In **Hoofdstuk XI** wordt de betekenis van de lymfografie in de diagnostiek van de retroperitoneale uitzaaiingen besproken. Alle lymfogrammen werden gereviseerd. Van de 95 beschikbare lymfogrammen waren er 86 bruikbaar voor dit onderzoek. Gecorreleerd met de bevindingen bij operatieen/of histologisch onderzoek, bleek er een betrouwbaarheid van 78% te bestaan. Indien het lymfografisch onderzoek als afwijkend werd geduid, was de betrouwbaarheid 88%, indien als normaal 74%.
Retroperitoneale lymfekliermetastasen werden bij 58% van de patienten met behulp van het lymfogram gevonden. Er bleek geen grens te zijn in grootte van de lymfeklier waarboven metastasen met zekerheid lymfografisch konden worden aangetoond.
Er konden geen verschillen worden aangetoond in de resultaten van behandeling, indien deze werden gecorreleerd met de wijze van stageren.
Wij menen, dat de lymfografie in de diagnostiek van de niet-seminoom testistumor slechts een beperkte waarde heeft.

In **Hoofdstuk XII** wordt nagegaan of de locale uitbreiding van de primaire tumor invloed heeft op de metastasering op afstand en de prognose. Uitgaande van de TNM-klassificatie bleek, dat binnen de tunica albuginea beperkt gebleven primaire tumoren (P1 en P2) vaker voorkomen in stadium I (65%) dan gezwellen die zich in de testisaanhangselen hebben uitgebreid (P3) (33%). In stadium IIA werden geen verschillen gevonden, doch in de stadia IIB en IIC bleek de P3 categorie in respectievelijk 55 en 78% van de gevallen voor te komen. Van de 22 patienten met orgaanmetastasen hadden er 2 (23%) categorie P1, 16 (73%) P3 en 1 (4%) P4a. Soortgelijke getallen werden ook gevonden in relatie met de overleving. Categorie P1 ging in 10% (5/48) van de gevallen gepaard met orgaanmetastasen, categorie P3 in 33% (16/48).
Hoewel de locale uitbreiding van de primaire tumor correleert met het optreden van orgaanmetastasen, menen wij dat een onderverdeling van het primaire gezwel zoals deze wordt voorgesteld door de U.I.C.C. (1979) niet nodig is, omdat het voorkomen van orgaanmetastasen eenzelfde correlatie vertoont met de retroperitoneale uitzaaiing. Een stadiumindeling, die alleen gebaseerd is op de retroperitoneale metastasering, is dus zeer goed bruikbaar.
Er bleek eveneens een correlatie te bestaan tussen het waarnemen van ingroei in bloed- en lymfevaten en het optreden van orgaanmetastasen. Bij ingroei bleek 38% van de patienten orgaanmetastasen te ontwikkelen, tegen

13% indien dit niet werd gevonden. Echter bijna de helft van de patienten met orgaanmetastasen hadden stadium IIC van de ziekte. Juist bij deze patienten was steeds retroperitoneaal tumorweefsel aanwezig, vanwaaruit metastasering kan zijn opgetreden.
Tenslotte bleek er een correlatie te bestaan tussen ingroei in bloed- en lymfevaten en de uitgebreidheid van retroperitoneale metastasering. Ook deze bevinding noopt ons er niet toe, dit verschijnsel steeds als aparte ongunstige factor te beschouwen. Wij menen, dat als rationele basis voor de stagering van de niet-seminoom testistumor de toestand van de retroperitoneale lymfeklieren bepalend is. De enige betrouwbare methode om dit vast te stellen is de laparotomie of zo mogelijk de retroperitoneale lymfeklierdissectie.

REFERENCES

Abelev GI, SD Perova, NI Khramkova, LA Postnikova and IS Irlin: Production of embryonal α-globulin by transplantable mouse hepatomas. Transplantation, 1963, 1, 174-180.

Abelev GI: α-Fetoprotein as a Marker of Embryo-specific Differentiations in Normal and Tumor Tissues. Transplant Rev, 1974, 20, 3-37.

Abell MR, JV Fayos and I Lampe: Retroperitoneal Geminomas (Seminomas) without evidence of testicular involvance. Cancer, 1965, 18, 273-290.

Adams HD and HH v Geertruyden: Neurologic complications of aortic surgery. Ann Surg, 1956, 144, 574-610.

Allhoff E, G. Mödder, R Engelking and J Heissing: Nukliddetektorgesteuerte radikale lymphadenektomie bei Non-Seminom-Hodentumoren. Urologe A, 1981, 20, 42-45.

Alpert ME, J Uriel and B de Nechaud: Alpha$_1$ Fetoglobulin in the diagnosis of human hepatoma. N Eng J Med, 1968, 278, 984-986.

Altman BL and M Malament: Carcinoma of the testis following orchiopexy. J Urol, 1967, 97, 498-503.

American Joint Committee for cancer staging and end results reporting. In: Manual for Staging of Cancer 1977.

Aristizabal S, JR Davis, RC Miller, MJ Moore, MLM Boone: Bilateral primary germ cell testicular tumors, report of four cases and review of the literature. Cancer, 1978, 42, 591-597.

Babaian RJ and DE Johnson: Management of Stages I and II Nonseminomatous Germ Cell Tumors of the Testis. Cancer, 1980, 45, 1775-1781.

Batata MA, FCH Chu, BS Hilaris, WF Whitmore Jr, H Grabstald and R. Golbey: TNM Staging of Testis Cancer. Int J Radiation Oncology Biol Phys, 1980, 6, 291-295.

Barringer BS and AL Dean: Radium therapy of teratoid tumors of the testicle. JAMA, 1921, 77, 1237-1240.

Beck PH and RE Stutzman: Complications of retroperitoneal lymphadenectomy for nonseminomatous tumors of the testis. Urology, 1979, 13, 244-247.

Béclère M: La radiothérapie des neoplasmes intra abdomineaux d'origine testiculaire. Bull Acad Med Paris, 1916, 76, 72-81.

Blandy JP, HF Hope-Stone and AD Dayan: In: Tumours of the Testicle. William Heinemann Medical Books Ltd, London, 1970, p. 21.

Blandy J, R Chapman, D Pollock and E Mooland: The Management of Tumors of the Testis. In: Controversy in Surgery. RL Varco and JP Delaney. Saunders, Philadelphia, 1976, p. 489.

Bland-Sutton J: An improved method of removing the testicle and spermatic cord for malignant disease. Lancet, 1909, 1406-1409.

Boden G and R Gibb: Radiotherapy and Testicular Neoplasms. Lancet, 1951, ii, 1195-1197.

Borsky AA: Diagnosis, staging and natural histoty of testicular tumors. Cancer, 1973, 32, 1202-1205.

Bosl GJ, PH Lange, LE Nochomovitz, A Goldmann, EE Fraley, J Rosai, K Johnson and BJ Kennedy: Tumor Markers in Advanced Nonseminomatous Testicular Cancer. Cancer, 1981, 47, 572-576.

Bracken RB and KD Smith: Is semen cryoperservation helpful in testicular cancer? Urology, 1980, 15, 581-583.

Bradfield JS, RO Hagen and DO Ytredal: Carcinoma of the testis: An analysis of 104 patients with germinal tumors of the testis other than seminoma. Cancer, 1973, 31, 633-640.
Braunstein GD, KR McIntire and TA Waldmann: Discordance of Human Chorionic Gonadotropin and α-fetoprotein in Testicular Teratocarcinomas. Cancer, 1973, 31, 1065-1068.
Brosman SA: Testicular tumors in prepubertal children. Urology, 1979, 13, 581-588.
Buck, AS, DT Schamber, JG Maier and EL Lewis: Supraclavicular Node Biopsy and Malignant Testicular Tumors. J Urol, 1972, 107, 619-621.
Busch FM and ES Sayegh: Roentgenographic visualisation of human testicular lymphatics: a preliminary report. J Urol, 1963, 89, 106-110.
Busch FM, ES Sayegh and OW Chenault Jr: Some uses of lymphangiography in the management of testicular tumors. J Urol, 1965, 93, 490-495.
Carleton RL, NB Friedman and EJ Bomze: Experimental teratomas of the testis. Cancer, 1953, 6, 464-473.
Carter SK and TH Wasserman: The chemotherapy of urologic cancer, 1975, 36, 729-743.
Castro JR: Lymphadenectomy and Radiation Therapy in malignant Tumors of the Testicle other than pure Seminomas. Cancer, 1969, 24, 87-91.
Catalona WJ and MA Rubenstein: An incision for extended suprahilar retroperitoneal lymphadenectomy. J Urol, 1978, 119, 316-319.
Cavalli F, S Monfardini and G Pizzocaro: Report on the International Workshop on Staging and Treatment of Testicular Cancer. Europ J Cancer, 1980, 16, 1367-1372.
Chavez CM: Lymphatic drainage of the testicle. In: Progress in lymphology. Thieme, Stuttgart, 1967, p. 191.
Chevassu M: Tumeurs du testicle. Thesis, Steinheil, Paris, 1906, p. 144.
Chevassu M: Le traitement chirurgical de cancers du testicule. Rev de Chir, 1910, 61, 628-660.
Chiappa S, C Uslenghi, G Bonadonna, P Marano and G Ravasi: Combined testicular and foot lymphangiography in testicular carcinomas. Surg Gynec Obstet, 1966, 123, 10-14.
Clemmesen J: Doubling of Morbidity from Testis Carcinoma in Copenhagen 1943-1962. Acta Path Microbiol Scandinav, 1968, 72, 348-349.
Coley WB: Cancer of the testis, 64 cases, 12 cases of the undescended testis. Ann Surg, 1915, 26, 40-73.
Collins DH and RCB Pugh: Classification and frequency of testicular tumours. In: The pathology of testicular tumours. Suppl. Brit J Urol, 1964, 35, 1-11.
Comisarow RH and H Grabstald: Re-exploration for retroperitoneal lymph node metastases from testis tumors. J Urol, 1976, 115, 569-571.
Cook FE, DD Lawrence, JR Smith and EFGritti: Testicular Carcinoma and Lymphangiography. Radiology, 1965, 84, 420-427.
Cooper JF, WF Leadbetter and R Chute: The thoracoabdominal approach for retroperitoneal gland dissection: its application to testis tumors. Surg Gynec Obstet, 1950, 90, 486-496.
Coupland GAE and TS Reeve: Paraplegia: A complication of excision of abdominal aortic aneurysm. Surgery, 1968, 64, 878-881.
Cuneo B: Note sur les lymphatiques du testicule. Soc anat, 1901, 105-111.
Delbet P: Epithélioma testiculaire gauche. Ablation de la tumeur et des ganglions lombo-aortiques. Guérison. Bull Mém Soc Chir Paris, 1910, 36, 236-262.
Dickson JA: Hyperthermia in the treatment of cancer. Lancet, 1979, i, 202-205.
Dixon, FJ and RA Moore: Testicular Tumors a clinicopathological study. Cancer, 1953, 6, 427-554.
Donohue RE, RR Pfister, JW Weigel and OG Stonington: Supraclavicular Node Biopsy in Testicular Tumors. Urology, 1977a, 9, 546-548.
Donohue JP: Retroperitoneal lymphadenectomy: The Anterior Approach Including Bilateral Suprarenal-Hilar Dissection. Urol Clin N Amer, 1977b, 4, 509-522.
Donohue JP, JM Perez, LH Einhorn: Improved management of non-seminomatous testis tumors. J Urol, 1979, 121, 425-428.

Donohue JP, LH Einhorn and SD Williams: Cytoreductive surgery for metastatic testis cancer: consideration of timing and extend. J Urol, 1980, 123, 876-880.
Dijkhuizen RF, FW George, S Kurohara, M Rotner, CR Sargent and JK Varney: The use of cobalt 60 telecurietherapy or X-Ray therapy with and without lymphadenectomy in the treatment of testis germinal tumors: a 20-year comparative study. J Urol, 1968, 100, 321-328.
Earle JD, MA Bagshaw and HS Kaplan: Supervoltage radiation therapy of the testicular tumors. Amer J Roentgen 1974, 117, 653-661.
Edson M: Testis Cancer: The pendulum swings. Experience in 430 patients. J Urol, 1979, 122, 763-765.
Einhorn LH and JP Donohue: Improved Chemotherapy in Disseminated Testicular Cancer. J Urol, 1977, 117, 65-69.
Einhorn LH and JP Donohue: Combinatión Chemotherapy in Disseminated Testicular Cancer: The Indiana University Experience. Sem Oncol, 1979a, 6, 87-93.
Einhorn LH and JP Donohue: Adjuvant Chemotherapy for Testicular Cancer: Is it Necessary. In: Adjuvant Therapy of Cancer II. eds. SE Jones and SE Salmon. Grune and Stratton, New York, 1979b, p. 329.
Ewing J: Teratoma Testis and its Derivation. Surg Gynec Obstet, 1911, 12, 230-261.
Fein RL and DO Taber: Foot lymphography in the testis tumor patient. A review of fifty cases. Cancer, 1969, 24, 248-255.
Fergusson JD: Tumours of the Testis. Brit J Urol, 1962, 34, 407-421.
Foulerton AGR: Chondrifying carcinoma. Arch Middelsex Hosp, 1905, 5, 234-277.
Fowler JE Jr, DG Mcleod and RE Stutzman: Critical apparaisal of routine supraclavicular lymph node biopsy in staging of testicular tumors. Urology, 1979, 14, 230-232.
Friedman NB: The comparative morphogenesis of extragenital and gonadal teratoid tumors. Cancer, 1951, 4, 265-276.
Friedman NB and RA Moore: Tumors of the testis. A report on 922 Cases. Milit Surg, 1946, 99, 573-593.
Fraley EE, K Kedia and C Markland: The Role of Radical Operation in the Management of Nonseminomatous Germinal Tumors of the Testicle in the Adult. In: Controversy in Surgery. RL Varco and JP Delaney. Saunders Company, Philadelphia, 1976, p. 482.
Fraley EE, C Markland and PH Lange: Surgical Treatment of Stage I and Stage II Nonseminomatous Testicular Cancer in Adults. Urol Clin N Amer, 1977, 4, 453-463.
Fraley EE, PH Lange and BJ Kennedy: Germ-cell testicular cancer in adults. (First of two Parts). New Eng J Med, 1979a, 301, 1370-1377.
Fraley EE, PH Lange and BJ Kennedy: Germ-cell testicular cancer in adults. (Second of Two Parts). New Eng J Med, 1979b, 301, 1420-1426.
Fraley EW, PH Lange, RD Williams and SA Ortlip: Staging of Early Nonseminomatous Germ-Cell Testicular Cancer. Cancer, 1980, 45, 1762-1767.
Gehring GG, FK Rodriquez and DM Woodhead: Malignant degeneration of cryptorchid testis following orchiopexy. J Urol, 1974, 112, 354-356.
Gennari L, A Balestrazzi, R Zucali, G Pizzocaro, F Concolino and U Veronesi: Surgical treatment of intestinal complication after radiotherapy and surgety for malignant lymphoma and carcinoma of the testis. Tumori, 1979, 65, 625-633.
Giel R, W Frankenberg, J Oldhoff, B Otten, E vd Ploeg, H Schraffordt Koops and A Vermey: De chirurg-oncoloog en de kwaliteit van het leven van zijn patienten. Ned T Geneesk, 1977, 121, 1315-1320.
Gilbert JB: Tumors of testis following mumps orchitis. Case report and review of 22 cases. J Urol, 1944, 51, 296-300.
Gilbert JB, JB Hamilton: Studies in malignant testis tumors. III-Incidence and Nature of Tumors in Ectopic Testes. Surg Gynec Obstet, 1940, 71, 731-743.
Golbey RB, THF Reynolds and D Vugrin: Chemotherapy of Metastatic Germ Cell Tumors. Sem Oncol, 1979, 6, 82-86.

Graham S and RW Gibson: Social epidemiology of cancer of the testis. Cancer, 1972, 29, 1242-1249.
Gray SW and JE Skandalakis: Embryology for Surgeons. Saunder Company, Philadelphia, 1972, p. 571.
Grumet RF and B MacMahon: Trends in mortality from neoplasms of the testis. Cancer, 1958, 11, 790-797.
Guba AM, F Lough, GJ Collins, M Feaster and NM Rich: Iatrogenic Internal Hernia Involving the Iliac Artery. Ann Surg, 1978, 188, 48-52.
Guinn GA: Treatment: surgical management. In: Testicular Tumors, 2nd ed. DE Johnson. Medical Examination Publishing co.inc. Flushing, New York, 1976, p. 177.
Hadziselimowic F, B Herzog and H Seguchi. Surgical Correction of Cryptorchidism at 2 Years. Electron Microscopic and Morphometric Investigation. J Ped Surg, 1975, 10, 19-26.
Haines JS and H Grabstald: Tumor formation in atrophic testes. Arch Surg, 1950, 60, 857-860.
Halsted WS: The results of operations for the care of cancer of the breast performed at the Johns Hopkins hospital from June, 1889 to January, 1894. Ann Surg, 1894, 20, 497-555.
Hamilton JB and JB Gilbert: Studies in Malignant Tumors of the Testis. IV. Bilateral Testicular Cancer. Cancer Res, 1942, 2, 125-129.
Hansmann GH and JW Budd: Massive unattached retroperitoneal tumors, an explanation of unattached retroperitoneal tumors based on remnants of the embryonic urogenital apparatus. Amer J Path, 1931, 7, 631-674.
Hausfeld KF and D Schrandt: Malignancy of testis following atrophy: report of three cases. J Urol, 1965, 94, 69-72.
Hendry WF, A Barret, TH McElwain, DM Wallace and MJ Peckham: The Role of Surgery in the Combined Management of Metastases from Malignant Teratomas of the Testis. Brit J Urol, 1980, 52, 38-44.
Herr HW, I Silber and DC Martin: Management of inguinal lymph nodes in patients with testicular tumors following orchidopexy, inguinal or scrotal operations. J Urol, 1973, 110, 223-224.
Hill JT: Misdiagnosis of testicular tumours. J Royal Soc Med, 1978, 71, 737-740.
Hinman F: The operative treatment of tumors of the testicle. With the report of thirty cases treated by orchidectomy. JAMA, 1914, 63, 2009-2015.
Hinman F: The radical operation for teratoma testis. With the report of five cases. Surg Gynec Obstet, 1919, 28, 495-508.
Hinman F, TE Gibson and AA Kutzmann: The Radical Operation for Teratoma Testis. Surg Gynec Obstet, 1923, 37, 429-451.
Hinman F: Tumors of the testis. Five year Cases Following Radical Operation. Surg Gynec Obstet, 1933, 56, 450-463.
Hinman F: The prognosis and treatment of tumors of the testis. J Urol, 1935, 34, 72-84.
Hoekstra HJ, Th Wobbes, ThM Brouwers, A Postma and H Schraffordt Koops: Embryonal rhabdomyosarcoma of spermatic cord. Urology, 1980, 16, 360-363.
Hoekstra HJ, Th Wobbes, DTh Sleyfer and H Schraffordt Koops: Bilaterale primaire kiemcel-tumoren van de testis. Ned T Geneesk, 1981, 125, 1188-1190.
Höffken K, J Tingelhoff, S Seeber and CG Schmidt: Actinomycin-D-Monotherapie bei malignen Hodentumoren. Urologe A, 1976, 15, 61-65.
Hoff DD von: New leads from the laboratory for treating testicular cancer. In: Therapeutic progress in Ovarian Cancer, Testicular Cancer and the Sarcomas. AT v Oosterom et al. (eds). Martinus Nijhoff Publishers, The Hague 1980, p. 226.
Hong WK, RE Wittes, ST Hajdu, E Cvitkovic, WF Whitmore and RB Golbey: The evolution of mature teratoma from malignant testicular tumors. Cancer, 1977, 40, 2987-2992.
Howard R: A radical operation for malignant disease of the testis. Lancet, 1910, 2, 1406-1408.
Hultén L, LG Kindblom, J Lindhagen, M Rosencrantz, T Seeman and L Wahlquist: Funicular and pedal lymphography in testicular tumours. Acta Chir Scand, 1973, 139, 746-758.

Husband JE, MJ Peckham, JS MacDonald and WF Hendry: The Role of Computed Tomography in the Management of Testicular Teratoma. Clin Radiol, 1979, 30, 243-252.
Husband JE, A Barret and MJ Peckham: Evaluation of Computed Tomography in the Management of Testicular Teratoma. Brit J Urol, 1981, 53, 179-183.
Hussey DH, KH Luk and DE Johnson: The Role of Radiation Therapy in the Treatment of Germinal Cell Tumors of the Testis Other than Pure Seminomas. Radiology, 1977, 123, 175-180.
Jacobs EM and FM Muggia: Testicular Cancer: Risk Factors and the Role of Adjuvant Chemotherapy. Cancer, 1980, 45, 1782-1790.
Jackson BT: The lumbar lymphatics: a lymphographic study. Ann Royal Coll Surg Eng, 1974, 54, 3-15.
Jamieson JK and JF Dobson: The lymphatics of the testicle. Lancet, 1910, 1, 493-494.
Javadpour N, KK McIntire, TA Waldmann and SM Bergman: The role of alpha-fetoprotein and human chorionic gonadotropin in seminoma. J Urol, 1978, 120, 687-690.
Javadpour N: The national cancer institute experience with testicular cancer. J Urol, 1978, 120, 651-659.
Johnson DE, JP Laneri, CF Mountain and M Luna: Extragonadal germ-cell tumors. Surgery, 1973, 73, 85-90.
Johnson DE: Testicular Tumors. Medical examination publishing co.inc. Flushing, New York, 1976.
Johnson DE, RB Bracken and EM Blight: Prognosis for pathologic stage I non-seminomatous germ cell tumors of the testis managed by retroperitoneal lymphadenectomy. J Urol, 1976, 116, 63-65.
Johnson DE: Retroperitoneal Lymphadenectomy: Indications, Complications and Expectations. Recent Results in Cancer Research, 1977, 60, 221-230.
Jonsson K, S Wallace, BS Jing, LE Boyle and DE Johnson: Lymphangiography in patients with malignancy in a non-descended testicle. J Urol, 1978, 119, 614-617.
Kademian M and G Wirtanen: Accuracy of bipedal lymphangiography in testicular tumors. Urology, 1977, 9, 218-220.
Kagan AR and DG Skinner: Detection of metastatic disease in the urologic patient: an opinion on cost versus benefit. J Urol, 1978, 120, 140-141.
Kaswick JA, SD Bloomberg and DG Skinner: Radical retroperitoneal lymph node dissection: how effective in removal of all retroperitoneal nodes? J Urol, 1976, 115, 70-72.
Kauffman JJ and PT Bruce: Testicular atrophy following mumps. A cause of Testis Tumour? Brit J Urol, 1963, 35, 67-69.
Kedia KR, C Markland and EE Fraley: Sexual Function Following high Retroperitoneal Lymphadenectomy. J Urol, 1975, 114, 237-239.
Kedia KR, C Markland and EE Fraley: Sexual Function after High Retroperitoneal Lymphadenectomy. Urol Clin N Amer, 1977, 4, 523-528.
Kinmonth JB: Lymphangiography in Man, Method of Outlining Lymphatic Trunk at Operation. Clin Sc, 1952, 11, 13-20.
Kocher Th: Die Krankheiten der männlichen Geslechtsorganen. Verlag von Ferdinand Enke, Stuttgart, 1887, p. 491.
Kohn JO, AH Orr, TJ McElwain, M Bentall and MJ Peckham: Serum-alpha$_1$-fetoprotein in patients with testicular tumors. Lancet, 1976, ii, 433-436.
Kom C, SG Mulholland and M Edson: Etiology of Infertility after Retroperitoneal Lymphadenectomy. J Urol, 1971, 105, 528-530.
Krabbe S, JG Berthelsen, P Volsted, J Eldrup, NE Skakkebæk, K. Mauritzen and AH Nielsen: High incidence of undetected neoplasia in maldescended testes. Lancet, 1979, i, 999-1000.
Kurman RJ, PT Scardino, KR McIntire, TA Waldmann and N Javadpour: Cellular Localisation of α-fetoprotein and H.G.C. in germ cell tumors of the testis using an indirect immunoperoxidase technique. Cancer, 1977, 40, 2136-2151.

Kurohara SS, FW George III, RF Dijkhuizen and KL Leary: Testicular Tumors, Analysis of 196 Cases Treated at the US Naval Hospital in San Diego. Cancer, 1967, 20, 1089-1098.
Lange PH, KR McIntire, TA Waldmann, TR Hakala and EE Fraley: Serum alpha fetoprotein and human chorionic gonadotropin in the diagnosis and management of nonseminomatous germ-cell testicular cancer. New Eng J Med, 1976, 295, 1337-1240.
LeComte PNO: Ectopies congéniales des testicules. Thesis, Faculté de Medicine de Paris, 1851, p. 7.
Leadbetter WF: Treatment of testis tumors based on their pathological behaviour. JAMA, 1953, 151, 275-280.
Lee JKT, McClennan, RJ Stanley and SS Sagel: Computed Tomography in the Staging of Testicular Neoplasms. Radiology, 1979, 130, 387-390.
Lewis LC: Testis tumors: Report on 250 cases. J Urol, 1948, 59, 763-772.
Lewis EL, RE Johnston, RB Rowe and JC Kimbrough: Retroperitoneal lymph node resection: the intercosto-inguinal approach. J Urol, 1952, 67, 338-341.
Leiter E and H Brendler: Loss of ejaculation following bilateral retroperitoneal lymphadenectomy. J Urol, 1967, 98, 375-378.
Li MC, WF Whitmore, R Golbey and H Grabstald: Effects of combined drug therapy on metastatic cancer of the testis. JAMA, 1960, 174, 145-153.
Lien HH and A Kolbenstvedt: Phlebography, urography and lymphography in the diagnosis of metastases from testicular tumors. Acta radiol Diagnosis, 1977, 18, 177-185.
Lindsey CM and JF Glenn: Germinal Malignancies of the Testis: experience, management and program. J Urol, 1976, 116, 59-62.
Lipworth L and AD Dayan: Rural preponderance of seminoma of the testis. Cancer, 1969, 23, 1119-1121.
Loening S, JD Schmidt, RC Brown, CE Hawtrey, B Fallon and DA Culp: A comparison between lymphangiography and pelvic node dissection in the staging of prostatic cancer. J Urol, 1977, 117, 752-755.
Luna MA and J Valenzuela-Tamariz: Germ-cell Tumors of the Mediastinum, Postmortem Findings. Amer J Clin Path, 1976, 450-454.
Lynch Jr DF, LP McCord, TC Nicholson, JP Richie and CR Sargentes: Sandwich therapy in testis tumor: current experience. J Urol, 1978, 119, 612-613.
MacKay EN and AH Sellers: A Statistical Review of Malignant Testicular Tumours Based on the Experience of the Ontario Cancer Foundation Clinics. Canad Med Ass J, 1966, 94, 889-899.
Macklin MT: An analysis of tumors in monzygos and dizygos twins, with a report of 15 unpublished cases. J Hered, 1940, 32, 277-290.
Martin DC and HK Menck: The undescended testis. Management after puberty. J Urol, 1975, 14, 77-79.
Maier JG, BT Mittemeyer and MH Sulak: Treatment and prognosis in seminoma of the testis. J Urol, 1968, 99, 72-78.
Maier JG and DT Schamber: The role of lymphangiography in the diagnosis and treatment of malignant testicular tumors. Amer J Roentgen, 1972, 114, 482-490.
Maier JG and B Mittemeyer: Carcinoma of the testis. Cancer, 1977, 39, 981-986.
Maier JG and SN Lee: Radiation Therapy for Non-seminomatous Germ Cell Testicular Cancer in Adults. Urol Clin N Amer, 1977, 4, 477-493.
Maier JG: Testis Carcinoma: What Role Radiotherapy? In: Cancer of the Genitourinary tract. DE Johnson and ML Samuels. Raven Press, New York, 1979, p. 139.
Mallis N and JF Patton: Transperitoneal Bilateral Lymphadenectomy in Testis Tumor. J Urol, 1958, 80, 501-503.
Marion M: Cancer du testicule. Extirpation avec ablation des ganglions lombo-aortiques par le procédé de Chevassu. Bull Mém Soc Chir Paris, 1910, 36, 1361-1367.
Markland C, K Kedia and EE Fraley: Inadequate Orchiectomy for Patients With Testicular Tumors. JAMA, 1973, 224, 1025-1026.

Mausler HM et al.: The intergroup rhabdomyosarcoma study, a preliminary report. Cancer, 1977, 40, 2015-2026.
Mengel W, HA Heinz, WG Sippe and WCh Hecker: Studies on Cryptorchidism: A Comparison of Histological Findings in the Germinative Epithelium Before and After the Second Year of Live. J Ped Surg, 1974, 9, 445-450.
Merrin CE and GP Murphy: Metastatic Testicular Carcinoma (Single-agent chemotherapy (actinomycin-D) in treatment). New York State J Med, 1974, april, 654-657.
Merrin C: Combination of chemotherapy and debulking surgery. In: Therapeutic progress in Ovarian cancer, Testicular cancer and the Sarcomas. ATv Oosterom et al. (eds). Martinus Nijhoff Publishers, The Hague, 1980, p. 211-224.
Moore MR, PR Garrett, KN Walton, TA Waldmann, RK McIntire, P Counts and CL Vogel: Evaluation of HCG and α-fetoprotein in benign and malignant testicular disorders. Surg Gynec Obstet, 1978, 147, 167-174.
Morris SA, ED Vaughan Jr and WC Constable: Problems in management of primary bilateral germ cell testicular tumors: report of 3 cases and review of literature. J Urol, 1976, 115, 566-568.
Morrison AS: Cryptorchidism, Hernia and Cancer of the Testis. J Nat Cancer Inst, 1976, 731-733.
Most: Ueber die Lymphgefässe und Lymphdrüsen des Hodens. Arch Path Anat Entwicklungsgeschichte, 1899, 113-123.
Mostofi JD and EB Price JR: Tumors of the male genital system. In: Atlas of tumor pathology, 2nd series, fasc 8, Armed Forces Inst. of Path., Washington, 1973.
Mostofi FK and LH Sobin: Histological typing of testis tumours. In: International histological classification of tumors. No 16. World Health Organization, Geneva, 1977.
Mostofi FK, Pathology of Germ Cell Tumors of Testis. A Program Report. Cancer, 1980, 45, 1735-1754.
Mustard WT, MM Ravitch, WH Snijder, RJ Welch and CD Benson. In: Pediatric Surgery, 2nd ed. Year Book Medical Publishers, Inc, Chicago, 1969, p. 692.
Narayana AS, S Loening and DA Culp: The Value of Alpha-fetoprotein and Beta-human Chorionic Gonadotrophin in the Management of Testicular Tumors. Brit J Urol, 1978, 50, 605-608.
Narayana AS, S Loening, G Weimar and DA Culp: Serum markers in testicular tumors. J Urol, 1979, 121, 51-53.
Nefziger MD and FK Mostofi: Survival after Surgery for Germinal Malignancies of the Testis. Cancer, 1972, 30, 1225-1232.
Newlands ES, J Dent, A Kardana, F Searle and KD Bagshawe: Serum α-fetoprotein and H.C.G. in patients with testicular tumors. Lancet, 1976, ii, 744-745.
Nicholson TC, PC Walsh and MB Roner: Lymphadenectomy combined with preoperative and postoperative Cobalt 60 teletherapy in the management of embryonal carcinoma and teratocarcinoma of the testis. J Urol, 1974, 112, 109-110.
Nijman JM, PW Boer, H Schraffordt Koops, J Oldhoff and J Kremer: Medicamenteuze behandeling van ejaculatiestoornissen na retroperitoneale lymfeklierdissectie wegens nonseminoma testistumor. Ned T Geneesk, 1981, 125, 1060.
Nochomovitz LE, FE De la Torre R and J Rosai: Pathology of Germ Cell Tumors of the Testis. Urol Clin N Amer, 1977, 4, 359-378.
Nochomovitz LE and J Rosai: Current concepts on the histogenesis, pathology and immunochemistry of germ cell tumors of the testis. Path Ann, 1978, 13, 327-362.
Oliver RTD and A Rohatiner: Chemotherapy of metastatic testicular tumours. Brit J Urol, 1980, 52, 34-37.
Oosterhuis JW, GJ Fleuren, J Oldhoff, H Schraffordt Koops, DTh Sleijfer: Differentiation in retroperitoneal metastases of non-seminomas of the testis after chemotherapy. Poster session, Int. Symp. on Human Testis Cancer. Minneapolis, June 1980.

Orbaan C: Behandeling der uitgebreide kwaadaardige gezwellen van de mannelijke en vrouwelijke geslachtsklieren met röntgenstralen. Ned T Geneesk, 1920, 2, 695-702.
Patton JF, CB Hewitt and N Mallis: Diagnosis and Treatment of Tumors of the Testis. JAMA, 1959, 171, 2194-2198.
Patton JF, DN Seitzman and RA Zone: Diagnosis and Treatment of Testicular Tumors. Amer J Surg, 1960, 99, 525-532.
Peckham MJ: An Appraisal of the Role of Radiation Therapy in the Management of Non-seminomatous Germ-Cell Tumors of the Testis in the Era of Effective Chemotherapy. Cancer Treat Rep, 1979, 63, 1653-1658.
Peckham MJ, A Barret, TJ McElwain and WF Hendry: Combined management of malignant teratoma of the testis. Lancet, 1979, ii, 267-270.
Pierce GB and MR Abell: Embryonal carcinoma of the testis. Path Ann, 1970, 5, 27-60.
Post GJ and JA Belis: Delayed Presentation of Testicular Tumors. South Med J, 1980, 73, 33-35.
Prout GR Jr: TNM Staging of Testis Cancer. Editorial. Int J Radiation Oncology Biol Phys, 1980, 6, 393-394.
Pugh RCB and KM Cameron: Teratomata. In: Pathology of the testis. RCB Pugh. Blackwell Scientific Publications, Oxford, 1976, p. 202.
Quivey JM, KK Fu, KA Herzog, JM Weiss and ThL Phillips: Malignant Tumors of the Testis: Analysis of Treatment Results and Sites and Causes of Failure. Cancer, 1977, 39, 1247-1253.
Raghavan D, T Jelihovsky and R Fox: Father-Son Testicular Malignancy. Does Genetic Anticipation Occur? Cancer, 1980, 45, 1005-1009.
Rao AB and B Spark: Tumours of Testis in Jamaica. Brit J Urol, 1979, 51, 151-153.
Ray B, SI Hajdu and WF Whitmore: Distribution of retroperitoneal lymph node metastases in testicular germinal tumors. Cancer, 1974, 33, 340-348.
Roberts JB: Excision of the lumbar lymphatic nodes and spermatic vein in malignant disease of the testicle. Ann Surg, 1902, 36, 539-549.
Rouvière H: Lymphatiques du testicule. In: Anatomie des lymphatiques de l'homme. Masson et Cie. Paris, 1932.
Safer ML, JP Green, QE Crews Jr. and DR Hill: Lymphangiographic accuracy in the staging of testicular tumors. Cancer, 1975, 35, 1603-1605.
Sago AL, TP Ball and DE Novicki: Complications of retroperitoneal lymphadenectomy. Urology, 1979, 13, 241-243.
Sandeman TF and JP Matthews: The staging of testicular tumors. Cancer, 1979, 43, 2514-2524.
Samuels ML, DE Johnson, B Brown, RB Bracken, ME Moran and A von Eschenbach: Velban Plus Continuous Infusion Bleomycin (VB-3) in Stage III Advanced Testicular Cancer: Results in 99 Patients with a Note on High-Dose Velban and Sequential Cisplatinum. In: Cancer of the Genitourinary Tract. DE Johnson and ML Samuels. Raven Press, New York, 1979a, p. 159-172.
Samuels ML, DE Johnson and RB Bracken: Adjuvant Chemotherapy in Metastatic Testicular Neoplasia: Results With Vinblastine-Bleomycin. In: Cancer of the Genitourinary Tract. DE Johnson and ML Samuels. Raven Press, New York, 1979b, p. 173-180.
Scardino PT, HD Cox, TA Waldmann, KR McIntire, B Mittemeyer and N Javadpour: The value of serum tumor markers in the staging and prognosis of germ cell tumors of the testis. J Urol, 1977, 118, 994-999.
Schlumberger HG: Teratoma of the anterior mediastinum in the group of the military age. Arch Path, 1946, 41, 398-444.
Schraffordt Koops H, R Eibergen, J Oldhoff and E vd Ploeg: Non-seminoma testistumoren; resultaten van een behandelingswijze waarin de retroperitoneale klierdissectie centraal staat. Ned T Geneesk, 1978, 122, 1020-1026.
Shinohara M, H Komatsu, T Kawamura and M Yokoyama: Familial testicular teratoma in 2 children: familial report and review of the literature. J Urol, 1980, 123, 552-555.

Simson LR, I Lampe and MR Abell: Suprasellar germinomas. Cancer, 1968, 22, 533-544.
Skakkebæk NE and JG Berthelsen: Carcinoma-in-situ of testis and orchiectomy. Lancet, 1978, ii, 204-205.
Skakkebæk NE and JG Berthelsen: Carcinoma-in-situ of the testis and invasive growth of different types of germ cell tumours. A revised germ cell theory. Int J Androl, 1981, Suppl. 4, 26-34.
Skinner DG: Non-seminomatous testis tumors: a plan of management based on 96 patients to improve survival in all stages by combined therapeutic modalities. J Urol, 1976a, 115, 65-69.
Skinner DG: Complications of lymph node dissection. In: Complications of urologic surgery, prevention and management. RB Smith and DG Skinner. W.B. Saunders, Philadelphia, 1976b, p. 423.
Skinner DG: Advances in the Management of Non-seminomatous Germinal Tumours of the Testis. Brit J Urol, 1977a, 49, 553-560.
Skinner DG: Consideration for Management of Large Retroperitoneal tumors. Use of the Modified Thoracoabdominal approach. J Urol, 1977b, 117, 605-609.
Skinner DG: Surgical Management of Advanced Nonseminomatous Tumors of the Testis. Urol Clin N Amer, 1977c, 4, 465-476.
Skinner DG: Role of surgery in the management of nonseminomatous germ cell tumors of the testis. In: Therapeutic Progress in Ovarian Cancer, Testicular Cancer and the Sarcomas. AT v Oosterom et al. (eds) Martinus Nijhoff Publishers, The Hague, 1980, p. 159-172.
Skinner DG and PT Scardino: Relevance of biochemical tumor markers and lymphadenectomy in management of non-seminomatous testis tumors: current perspective. J Urol, 1980, 123, 378-382.
Smithers DW: The management of patients with tumours of the testis. In: Pathology of the testis. RCP Pugh. Blackwell Scientific Publications, Oxford, 1976, p. 409.
Staubitz WJ, KS Early, IV Magoss and GP Murphy: Surgical treatment of non-seminomatous germinal testes tumors. Cancer, 1973, 32, 1206-1211.
Staubitz WJ, KS Early, IV Magoss and GP Murphy: Surgical Management of Testis Tumor. J Urol, 1974, 111, 205-209.
Staubitz WJ: Surgical Treatment of Nonseminomatous Germinal Testis Tumors. In: Cancer of the Genitourinary tract. DE Johnson and ML Samuels. Raven Press, New York, 1979, p. 135-138.
Stehlin JS, JS Jones, DM Crigler and O Creech: Lymphadenectomy via the Transperitoneal (Anterior Abdominal) Approach for Cancer of the Testis. Am J Surg, 1959, 97, 756-765.
Storm PB, A Kern, SA Loening, RC Brown and DA Culp: Evaluation of pedal lymphangiography in staging non-seminomatous testicular carcinoma. J Urol, 1977, 118, 1000-1003.
Stoter G, CPJ Vendrik, A Struyvenberg, ThM Brouwers, DTh Sleyfer, H Schraffordt Koops, AT v Oosterom and HM Pinedo: Combination chemotherapy with cis-diamminedichloroplatinum, vinblastine, and bleomycine in advanced testicular non-seminoma. Lancet, 1979, i, 941-945.
Talerman A, JGAH Kaalen en W Fokkens: Rural Preponderance of testicular Neoplasms. Br J Cancer, 1974, 29, 176-178.
Talerman A: The incidence of yolk sac tumor (endodermal sinus tumor) elements in germ cell tumors of the testis in adults. Cancer, 1975, 36, 211-215.
Tavel FR, ThG Osius, JF Parker, RB Goodfriend, DF McGonigle, MP Jassie, EL Simmons, MI Tobenkin and JW Schutte: Retroperitoneal lymph node dissection. J Urol, 1963, 89, 241-245.
Teilum G, R Albrechtsen and B Nørgaard-Pedersen: The histogenetic-embryologic basis for reappearance of alpha-fetoprotein in endodermal sinus tumors (yolk sac tumors) and teratomas. Acta Path Microbiol Scand, Sect. A, 1975, 83, 80-86.
Teppo L: Testicular Cancer in Finland. Acta Path Microbiol Scand, Suppl., 1973, 238, p. 38.

Thompson IM, J Wear Jr, C Almond, EJ Schewe and J Sala: An analytical survey of one hundred and seventy-eight testicular tumors. J Urol, 1961, 85, 173-179.
Tierie AH, JJ Batterman and G Hart: Radiotherapie van Testistumoren. Tijdschrift Kanker, 1978, 3, 22-23.
Tyrrell CJ and MJ Peckham: The Respons of Lymph Node Metastases of Testicular Teratoma to Radiation Therapy. Brit J Urol, 1976, 48, 363-370.
Tyrrell CJ, DO Cosgrove, VR McCready and MJ Peckham: The role of ultrasound in the assessment and treatment of abdominal metastases from testicular tumours. Clin Radiol, 1977, 28, 475-481.
UICC, TNM Klassification der Malignen Tumoren, 3nd ed. Springer Verlag, Berlin, 1979.
Vallet BS: The Nagamatsu technique applied to retroperitoneal dissection in testis tumor. J Urol, 1952, 68, 337-339.
Villar F: Methode rationelle de castration dans les cas de tumeurs malignes du testicule. Congres Francais de Chirurgie, 1902, 15, 714-729.
Vugrin D, E Cvitkovic, WJ Whitmore and RB Golbey: Adjuvant Chemotherapy in Resected Nonseminomatous Germ Cell Tumors of Testis: Stages I and II. Sem Oncol, 1979, 6, 94-98.
Wallace S, L Jackson, B Schaffer, J Gould, RR Greening, A Weiss and S Kramer: Lymphangiograms: Their Diagnostic and Therapeutic Potential. Radiology, 1961, 76, 179-199.
Wallace S and BS Jing: Lymphangiography: Diagnosis of Nodal Metastases from Testicular Malignancies. JAMA, 1970, 213, 94-96.
Waldman TA and KR McIntire: Serum-alpha-fetoprotein levels in patients with ataxia-telangiectasia. Lancet, 1972, ii, 1112-1115.
Waldman TA and KR McIntire: The use of a radioimmunoassay for alpha-fetoprotein in the diagnosis of malignancy. Cancer, 1974, 34, 1510-1515.
Walsh PC, JJ Kaufman, WF Coulson and WE Goodwin: Retroperitoneal Lymphadenectomy for Testicular Tumors. JAMA, 1971, 217, 309-312.
Werf-Messing B vd: Radiotherapeutic treatment of testicular tumors. Int J Radiation Oncology Biol Phys, 1976, 1, 235-248.
Werf-Messing BHP vd: Role of radiotherapy in the treatment of testicular cancer. In: Therapeutic Progress in Ovarian Cancer, Testicular Cancer and the Sarcomas. AT v Oosterom et al. (eds). Martinus Nijhoff Publishers, The Hague, 1980, p. 173-180.
Whitmore WF Jr: Germinal Tumors of the Testis: Proceeding 6th Nat. Cancer Conf. Lippincot, Denver, 1970, p. 219.
Williams SD, LH Einhorn and JP Donohue: Testicular Cancer: The Indiana University experience. In: Therapeutic progress in Ovarian Cancer, Testicular Cancer and the Sarcomas. AT v Oosterom et al. (eds). Martinus Nijhoff Publishers, The Hague, 1980, p. 195-202.
Williams RD, SB Feinberg, LC Knight and EE Fraley: Abdominal staging of testicular tumors using ultrasonography and computes tomography. J Urol, 1980, 123, 872-875.
Wilbur HJ, MW Woodraf and MS Welch: Concomittant germ cell tumors in monozygotic twins. J Urol, 1979, 121, 538-540.
Willemse PHB, DTh Sleijfer, H Schraffordt Koops, HWA de Bruijn, JW Oosterhuis, ThM Brouwers, Th Ockhuizen and J Marrink: Tumor markers in patients with non-seminomatous germ cell tumors of the testis. Oncodev. Biol. Med, 1981, 2, 117-128.
Willis RA: Pathology of Tumors. Butterworths, London, 1960, p. 558.
Witus WS, JH Sloss and WL Valk: Inguinal Node Metastases from Testicular tumors developing after orchiopexy. J Urol, 1959, 81, 669-671.
Wobbes Th: Extragonadal germ-cell tumours. Arch Chir Neerl, 1976, 31, 101-106.
Wobbes Th: Gynaecomastie, alleen een psychologisch prbleem? Ned T Geneesk, 1980, 124, 305-308.
Wobbes Th, H Schraffordt Koops and J Oldhoff: The Relation Between Testicular Tumours, Undescended Testes and Inguinal Hernias. J Surg Oncol, 1980a, 14, 45-51.

Wobbes Th, H Schraffordt Koops and J Oldhoff: Het verband tussen maligne testistumoren, niet-ingedaalde testes en liesbreuken. Ned T Geneesk, 1980b, 124, 2030-2034.
Wobbes Th, HJ Hoekstra, DTh Sleyfer and H Schraffordt Koops: Tumours of the Testis in Two Brothers: a case report. J Surg Oncol, 1981a, 17, 135-137.
Wobbes Th, H Schraffordt Koops, J Oldhoff and JA de Vries: The treatment of infantile embryonal carcinoma (yolk-sac tumour) of the testis in children. Z Kinderchir, 1981b, 33, 349-354.
Zaunbauer W, R Kunz and R Leuppi: Die diagnostische Zuverlässigkeit der Lymphographie bei Patiënten mit malignen Hodentumoren. Fortschr Röntgenstr, 1977, 126, 335-338.
Zimmerman RR and A Kung'u: Testicular neoplasms in Kenyan Africans. Cancer, 1978, 41, 2452-2455.